Pekka Jylhä

Depression, Anxiety, Psychiatric Comorbidity and Dimensions of Temperament and Personality

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DEPRESSION, ANXIETY, PSYCHIATRIC COMORBIDITY AND DIMENSIONS OF TEMPERAMENT AND PERSONALITY

Pekka Jylhä

Academic Dissertation

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To Seija, Joel, Lauri and Tuomas

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TIIVISTELMÄ

Tämä tutkimus on osa Kansanterveyslaitoksen Mielenterveyden ja Alkoholitutkimuksen osaston Mielialahäiriöprojektia. Tutkimus koostuu 441 espoolaisen ja vantaalaisen henkilön yleisväestöotoksesta ja 269 vakavaa masennusta sairastavan vantaalaisen psykiatrisen avohoito- ja sairaalapotilaan etenevästä kohorttitutkimuksesta (Vantaa Depression Study, VDS).

Yleisväestötutkimusta varten Väestörekisteristä seulottiin 900 henkilön otos (300 Espoosta, 600 Vantaalta), iältään 20-70 vuotiaita, joille lähetettiin kysymyslomakkeisto, joka sisälsi sosiodemograafisten kysymysten lisäksi asteikot mm ahdistuneisuuden (Beck Anxiety Inventory, BAI), masennuksen (Beck Depression Inventory, BDI) ja temperamentti- ja persoonallisuudenpiirteiden (Temperament and Character Inventory – Revised, TCI-R ja Eysenck Personality Inventory, EPI) mittaamista varten. Kaikkiaan 441 henkilöä vastasi (94 palautti ainoastaan lyhennetyn version, ilman TCI-R lomaketta) ja antoi suostumuksensa tutkimukseen.

Vantaa Depression Study:ssa 806 aikuispotilasta, iältään 20-59 vuotta, seulottiin depressiivisten oireiden osalta ja 542 haastateltiin puolistrukturoidulla haastattelumenetelmällä (SCAN). Tutkimukseen valikoitui 269 potilasta, jotka täyttivät ajankohtaisen vakavan masennustilan oirekriteerit. Heidät haastateltiin puolistrukturoiduin haastattelumenetelmin myös muiden psykiatristen häiriöiden poissulkemiseksi. Poissulkukriteereinä olivat kaksisuuntainen mielialahäiriö (tyyppi I ja II), skitsoaffektiivinen häiriö, skitsofrenia ja muut psykoosit sekä orgaaninen tai kemiallisen aineen aiheuttama mielialahäiriö. Nyt kyseessä olevaan tutkimukseen sisältyvät ne 193 potilasta (naisia 139, miehiä 54), jotka osallistuivat sekä 6 kk että 18 kk seurantoihin ja joiden masennus pysyi unipolaarisena seuranta-aikana. Potilaiden persoonallisuudenpiirteitä arvoitiin EPI:n avulla.

Yleisväestössä temperamentti- ja persoonallisuudenpiirteet liittyivät sekä masennus- että ahdistuneisuusoireisiin. Korkeat vaikeuksien välttämis (Harm Avoidance, HA)- ja matalat itseohjautuvuus (Self-Directedness, SD)-pisteet yhdistyivät kohtalaisesti, kun taas matalat extraversio (E)- ja korkeat neurotisismi (N)-pisteet vahvasti koettuihin

masennusja ahdistuneisuusoireisiin. Temperamentti- ja persoonallisuudenpiirteet, erityisesti korkeat HA-, matalat SD- ja korkeat N-pisteet ennustivat myös jossain määrin vastaajan itseilmoittamaa, psykiatrisista syistä tapahtunutta terveyspalvelujen käyttöä ja vastaajalla todettuja mielenteveyshäiriötä. Lisäksi korkeat HA-pisteet assosioituivat vastaajan sukulaisilla todettuihin mielenteveyshäiriöihin.

Masennuspotilailla N-pisteet alenivat huomattavasti ja E-pisteet nousivat jonkinverran masennuksesta toipumisen myötä. Masennus- ja ahdistuneisuusoireiden muutos seurannan aikana ennusti vain 1/3 siitä, mitä alkutilan N-pisteet ennustivat 18 kk:n N-pisteistä. Verrattuna N-pisteisiin, E-pisteet eivät näyttäneet olevan tilariippuvaisia ahdistuneisuus-oireista ja muutos masennusoireissa seurannan aikana selitti vain 1/20 osan siitä, mitä alkutilan E-pisteet ennustivat 18 kk:n E-pisteistä. Sairastettu masennusjakso, yhden vuoden seurannan aikana, ei näyttänyt muuttavan persoonallisuutta. Masennuspotilailla havaittiin selkeästi korkeammmat N-pisteet ja lievästi matalammat E-pisteet kuin yleisväestön edustajilla, senkin jälkeen kun masennus- ja ahdistuneisuusoireet oli vakioitu.

Masennuspotilailla ilmeni positiivinen annos-vaikutus – suhde N-pisteiden ja sekä I että II-akselin komorbidien sairauksien esiintyvyyden ja lukumäärän välillä. Negatiivinen vastaava suhde ilmeni puolestaan E-pisteiden ja komorbidin sosiaalisen fobian ja klusteri C:n esiintyvyyden välillä.

Tutkimus vahvisti käsitystä, että ahdistuneisuus- ja erityisesti masennustilat muodostavat jatkumon lievemmistä oireista vakavampaan tautitilaan. Masennuspotilailla löydökset tukevat sen lisäksi olettamusta, että korkeat N-pisteet ja jossain määrin myös matalat E-pisteet saattavat olla haavoittuvuustekijöitä vakavalle masennukselle ja että korkeat N- ja matalat E-pisteet altistavat vakavaa masennusta sairastavat potilaat komorbideille psykiatrisille sairauksille.

Asiasanat: masennus, ahdistuneisuus, vakava masennus, ahdistuneisuushäiriö, komorbiditeetti, persoonallisuudenpiirteet, persoonallisuus

ABBREVIATIONS

ANOVA	Analysis of Variance
APA	American Psychiatric Association
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
C	Co-operativeness
CDS	Collaborative Depression Study
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
DRD4	Dopamine receptor, subtype D4
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
E	Extraversion
ECA	Epidemiological Catchment Area Study
EPI	Eysenck Personality Inventory
EPQ	Eysenck Personality Questionnaire
ESEMeD	European Study of the Epidemiology of Mental Disorders
FINHCS	Finnish Health Care Survey
GABA	Gamma-aminobutyric acid
GAD	Generalized Anxiety Disorder
GRIK4	Glutamate receptor, ionotrophic, kainate 4
HA	Harm Avoidance
HAM-D	Hamilton Rating Scale for Depression
HPA	Hypothalamic-pituitary-adrenal
5-HT	5-hydroxytryptamine (Serotonin)
5-HTR2A	5-hydroxytryptamine receptor 2A
5-HTT	5-hydroxytryptamine transporter (Serotonin transporter)
5-HTTLPR	5-hydroxytryptamine transporter gene-linked polymorphic region
HUCH	Helsinki University Central Hospital
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases, 10th edition
ICD-11	International Classification of Diseases, 11th edition
M-CIDI	Munich-Composite International Diagnostic Interview
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder

MDE	Major Depressive Episode
N	Neuroticism
NA	Negative Affectivity
NCS	National Comorbidity Survey
NCS-R	National Comorbidity Survey Replication
NE	Negative Emotionality
NEO-PI-R	Five-Factor Personality Inventory - Revised
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NIMH	National Institute of Mental Health
NS	Novelty Seeking
OCD	Obsessive Compulsive Disorder
OHS	Ontario Health Survey
ODIN	European Outcome of Depression International Network
OR	Odds Ratio
P	Persistence
PA	Positive Affectivity
PANAS	Positive and Negative Affect Schedule
PC-VDS	Primary Care – VDS
PE	Positive Emotionality
PMCD	Peijas Medical Care District
PTSD	Posttraumatic Stress Disorder
RD	Reward Dependence
SCAN	Schedules for Clinical Assessment of Neuropsychiatry
SCID-II	Structured Clinical Interview for DSM-III-R personality disorders
sd	Standard deviation
SD	Self-Directedness
SPSS	Statistical Package for the Social Sciences for Windows
STAR-D	Sequenced Treatment Alternatives to Relieve Depression
ST	Self-Transcendence
TCI-R	Temperament and Character Inventory - Revised
UM-CIDI	University of Michigan – CIDI
VDS	Vantaa Depression Study
WHO	World Health Organization
ZKPQ	Zuckerman and Kuhlman's Personality Inventory
ZUNG SDS	Zung Self-Rating Depression Scale

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1. ABSTRACT

This study is part of the Mood Disorders Project conducted by the Department of Mental Health and Alcohol Research, National Public Health Institute, and consists of a general population survey sample and a major depressive disorder (MDD) patient cohort from Vantaa Depression Study (VDS). The general population survey study was conducted in 2003 in the cities of Espoo and Vantaa. The VDS is a collaborative depression research project between the Department of Mental Health and Alcohol Research of the National Public Health Institute and the Department of Psychiatry of the Peijas Medical Care District (PMCD) beginning in 1997. It is a prospective, naturalistic cohort study of 269 secondary-level care psychiatric out- and inpatients with a new episode of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) MDD.

In the general population survey study, a total of 900 participants (300 from Espoo, 600 from Vantaa) aged 20-70 years were randomly drawn from the Population Register Centre in Finland. A self-report booklet, including the Eysenck Personality Inventory (EPI), the Temperament and Character Inventory-Revised (TCI-R), the Beck Depression Inventory and the Beck Anxiety Inventory was mailed to all subjects. Altogether 441 participants responded (94 returned only the shortened version without TCI-R) and gave their informed consent.

VDS involved screening all patients aged 20-60 years (N=806) in the PMCD for a possible new episode of DSM-IV MDD. 542 consenting patients were interviewed with a semi-structured interview (the WHO Schedules for Clinical Assessment in Neuropsychiatry, version 2.0). 269 patients with a current DSM-IV MDD were included in the study and further interviewed with semi-structured interviews to assess all other axis I and II psychiatric diagnoses. Exclusion criteria were DSM-IV bipolar I and II, schizoaffective disorder, schizophrenia or another psychosis, organic and substance-induced mood disorders. In the present study are included those 193 (139 females, 54 males) individuals who could be followed up at both 6 and 18 months, and their depression had remained unipolar. Personality was investigated with the EPI.

Temperament and personality dimensions associated not only to the symptoms of depression, but also to the symptoms of anxiety among general population and in depressive patients, as well as personality dimensions to comorbid disorders in MDD patients, supporting the dimensional view of depression and anxiety. Among the general population High Harm Avoidance and low Self-Directedness associated moderately, whereas low extraversion and high neuroticism strongly with the depressive and anxiety symptoms. The temperament and personality dimensions, especially high Harm Avoidance, low Self-Directedness and high neuroticism were also somewhat predictive of self-reported use of health care services for psychiatric reasons, and lifetime mental disorder. Moreover, high Harm Avoidance associated with a family history of mental disorder.

In depressive patients, neuroticism scores were found to decline markedly and extraversion scores to increase somewhat with recovery. The predictive value of the changes in symptoms of depression and anxiety in explaining follow-up neuroticism was about 1/3 of that of baseline neuroticism. In contrast to neuroticism, the scores of extraversion showed no dependence on the symptoms of anxiety, and the change in the symptoms of depression explained only 1/20 of the follow-up extraversion compared with baseline extraversion. No evidence was found of the ’scar effect’ during a one-year follow-up period. Finally, even after controlling for symptoms of both depression and anxiety, depressive patients had a somewhat higher level of neuroticism (odds ratio 1.11, $p=0.001$) and a slightly lower level of extraversion (odds ratio 0.92, $p=0.003$) than subjects in the general population.

Among MDD patients, a positive dose-exposure relationship appeared to exist between neuroticism and prevalence and number of comorbid axis I and II disorders. A negative relationship existed between level of extraversion and prevalence of comorbid social phobia and cluster C personality disorders.

Personality dimensions are associated with the symptoms of depression and anxiety. Futhermore these findings support the hypothesis that high neuroticism and somewhat low extraversion might be vulnerability factors for MDD, and that high neuroticism and low extraversion predispose to comorbid axis I and II disorders among patients with MDD.

Keywords: depression, depressive disorder, anxiety, anxiety disorders, comorbidity, personality, neuroticism, extraversion

2. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals:

I Jylhä P, Isometsä E. Temperament, character and symptoms of anxiety and depression in the general population.
European Psychiatry 2006; 21:389-395.

II Jylhä P, Isometsä E. The relationship of neuroticism and extraversion to symptoms of anxiety and depression in the general population.
Depression and Anxiety 2006; 23:281-289.

III Jylhä P, Melartin T, Rytsälä H, Isometsä E. Neuroticism, Introversion and Major Depressive Disorder – Traits, States or Scars?
Depression and Anxiety (In Press).

IV Jylhä P, Melartin T, Isometsä E. Relationships of neuroticism and extraversion with axis I and II comorbidity among patients with DSM-IV major depressive disorder.
Manuscript (Submitted).

3. INTRODUCTION

Major depressive disorder (MDD) is a complex, highly prevalent, aetiologically multifactorial, clinically heterogeneous and often recurrent or chronic severe psychiatric disorder with considerable impairment in occupational and psychosocial functioning and increased rate of completed suicides. According to the WHO World Health Survey, depression produces the greatest decrement in health compared with the chronic diseases angina, arthritis, asthma and diabetes (Moussavi et al. 2007) and by the year 2020 will be second only to cardiovascular illness in the total disease burden imposed on humankind worldwide (Murray and López 1996).

In Finland the point prevalence of major depression is approximately 5%, corresponding to about 200 000 - 240 000 Finns (Pirkola et al. 2005). Elevated suicidality has been associated with major depression and anxiety disorders, resulting in about 750 completed suicides in Finland annually. According to the Social Insurance Institution in Finland, depression is also a major cause of functional and work disability. In 2005, due to MDD, 28 919 Finns were in a disability pension and 19 812 new sickness allowance spells were begun in Finland.

Personality refers to a consistent pattern in the way an individual behaves, feels and thinks, whereas temperament can be seen as the early appearing biological core of later adult personality. Temperament and personality dimensions have been studied using various self- and peer-rated questionnaires including the Eysenck Personality Inventory (EPI, Eysenck and Eysenck 1964) and the Temperament and Character Inventory (TCI, Cloninger et al. 1993) and its revised version, TCI-R.

The possible links between temperament and personality and mood has been examind since Hippocrates. Epidemiological (Hasin et al. 2005) and clinical (Melartin et al. 2002) studies have revealed that about 40-50% of patients with MDD have also a comorbid personality disorder. Theoretically personality may be involved in the pathogenesis of the disorder in multiple ways. Personality features may predispose an individual to, be shaped by repeated episodes of the illness, modify the clinical picture of the depressive illness or be an attenuated expression of the disorder (Shea and Yen 2005). Confusingly anxiety states may also affect on the assessment of the relationship between personality and depression (Reich et al. 1986). Thus, the investigation of the relationship between personality and major depressive disorder is complex.

The present thesis consists of a general population study and a clinical cohort study. Among the general population the relationship between temperament and personality dimensions, as measured with TCI-R and EPI, and the symptoms of depression and anxiety are studied. The relationship between the personality dimensions of neuroticism and extraversion, and pure MDD or with comorbid axis I or II disorder, are investigated among patients from The Vantaa Depression Study (VDS) as compared with the general population. VDS is a prospective, naturalistic cohort study of secondary-level care psychiatric out- and inpatients with a new episode of DSM-IV MDD.

4. REVIEW OF THE LITERATURE

4.1 Toward dimensional diagnostic concept of mood and anxiety disorders

Traditionally the diagnoses in psychiatry have been categorical. A patient either meets or fails to meet the relevant criteria for specific diagnoses. The introduction of operationalized classification systems for mental disorders, such as DSM-III (American Psychiatric Association 1980), DSM-IV (American Psychiatric Association 1994) and ICD-10 (World Health Organization 1992, 1993), have made a significant contribution to the scientific development of psychiatry by utilising objective, operationalized criteria of psychiatric diagnoses with specific thresholds and thus improving e.g. the diagnostic reliability, teaching of students and communication among scientists and the public (Kendell and Jablensky 2003). Likewise, categorical diagnoses have helped the clinicians to make decisions whether to treat, type of treatment etc. (Kraemer et al. 2004). However, the construct validity of the present DSM system is not well established (Spitzer and Williams 1985) and by using this categorical system a lot of clinically and scientifically important information of the patient is lost (Helzer et al. 2006).

As the processes toward developing DSM-V and ICD-11 progress, it has been increasingly acknowledged that not only categorical, but also dimensional approaches to a diagnosis is important for clinical work and research (Goldberg 2000; Haslam 2003; First 2006; Helzer et al. 2006). Dimensional system takes into account that there may be clinically important individual differences among those who fall above, and those who fall below, a categorical diagnostic threshold (Helzer et al. 2006). These differences e.g. number of positive symptoms, the severity of symptoms or comorbidity, may be presented on a scale ranging from a three-point ordinal measure to a continuum (Helzer et al. 2006). There are several potential benefits of dimensional expansion of a categorical diagnosis, including diagnosis-specific quantitative score, increased statistical power in research, new perspectives about the taxonomic problem of comorbidity and better understanding of public health and epidemiological data (Helzer et al. 2006). Practicing clinicians are more or less already accustomed to adopting a dimensional perspective (e.g. severity of illness) in clinical practice in order to develop a treatment plan and to assess clinical progress (van Os et al. 1996). However, as depression is a heterogeneous and an aetiologically multifactorial disorder, the sheer enumeration of symptoms and episodes, and their severity, does not give a full picture of depression or of the depressive patient. In addition to a clinical diagnosis, factors including life-events, personality, values and life goals should be incorporated into the evaluation of the patient.

4.2 Depression as a dimensional concept

4.2.1 Depression as an emotion

Depressive affect or feeling is a normal response to disappointment, loss or other painful events of human life. Depressive affects are self-limited and do not usually significantly interfere with a person's functional capacity, unless becoming longer lasting (American Psychiatric Association 2000b). Moreover, it has been postulated that in some situations the depressive mood might even be useful and have offered a selective advantage in humans' evolutionary history, by disengaging former goals and reallocating resources (Nesse 2006).

4.2.2 Symptoms of depression

Depressive symptoms include, among others, mood bias toward negative emotions (depressed mood), impaired reward function (anhedonia, lack of reactivity and loss of interest) and psychomotor symptoms (Hasler et al. 2004). The symptoms of depression are probably heterogeneous with respect to etiology and pathophysiology (Hasler et al. 2004). Moreover, depression itself has been found to be dynamic in nature, evolving on a continuous scale, ranging from no depressive symptoms, depressive symptoms, minor depression and finally to major depressive disorder (Kendler and Gardner 1998; Kessing 2007). In addition, the symptoms of depression measured cross-sectionally might change over time in the individual patient, fulfilling criteria for major depression, minor depression, dysthymia and subsyndromal states (Judd et al. 1997, 1998; Vuorilehto et al. 2005).

4.2.2.1 Measures of symptoms of depression

Depressive symptoms can be measured by using not only numerous disorder specific scales, but also by general measures. These general, non-disorder specific scales includes diagnostic interviews and general psychiatric symptoms measures.

4.2.2.1.1 Diagnostic interviews

The primary goal of diagnostic interviews is to provide some level of structure to the diagnostic assessment process by covering either DSM or ICD symptoms of various psychiatric disorders, including depression. Interviews that were designed to be used primarily in a psychiatric environment by mental health professionals, and to provide diagnosis according to DSM IV, include the Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-I, First et al. 1995) and interviews to provide diagnosis according to both ICD-10 and DSM-IV criteria include the Schedules for Clinical Assessment in Neuropsychiatry (SCAN, WHO 1994). Interviews that were designed to be used primarily in epidemiological studies by lay interviewers and to provide diagnosis according to DSM IV include the Diagnostic Interview Schedule (DIS, Robins et al. 1981), and measures to

provide diagnosis according to both ICD-10 and DSM-IV criteria include the Composite International Diagnostic Interview (CIDI, Robins et al. 1988). Interviews that were designed to be used in both clinical and epidemiological settings by lay interviewers and to provide diagnosis according to both ICD-10 and DSM-IV include the The Mini-International Neuropsychiatric Interview (MINI, Sheehan et al. 1998). Interviews that were first developed for the primary care settings include the Primary Care Evaluation of Mental Disorders (PRIME-MD, Spitzer et al. 1994) and the Symptom-Driven Diagnostic System for Primary Care (SDDS-PC, Olfson et al. 1995).

4.2.2.1.2 General psychiatric symptoms measures

The general psychiatric symptoms measures are intended as screening instruments to identify individuals most likely to have psychopathology, not as specific diagnostic measures. These scales include the Mental Health Inventory (MHI, Veit and Ware 1983); the General Health Questionnaire (GHQ, Goldberg 1972); the Symptom Checklist-90 (SCL-90, Derogatis et al. 1973) and its revised version SCL-90-R (Derogatis 1977); Brief Symptom Inventory (BSI, Derogatis and Melisaratos 1983) and the Patient Health Questionnaire-9 (PHQ-9, Spitzer et al. 1999), a self-report part of the PRIME-MD.

4.2.2.1.3 Specific depressive symptoms measures

To measure mood symptoms, numerous self-report and clinician-administered scales have been developed. There are several self-report measures that are commonly used either for screening depressive illness in the community or in the general medical population, including the Beck Depression Inventory (BDI, Beck et al. 1961), the Zung Self-Rating Depression Scale (Zung SDS, Zung 1965), the Centre for Epidemiologic Studies Depression Scale (CES-D, Radloff 1977), the Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith 1983) and the Depression Scale (DEPS, Salokangas et al. 1995; Poutanen et al. 2007). Additionally self-report rating scales for use in specific populations have been developed, including the Edinburgh Postnatal Depression Scale (EPDS, Cox et al. 1987) as a screening test for postpartum depression and the Geriatric Depression Scale (GDS, Yesavage and Brink 1983) as a screening test for depression in elderly people. Some of the self-administered mood disorders measures, including the BDI, Zung SDS and CES-D, are also used to measure the severity of depressive symptoms.

Observer-rated depressive symptom scales designed to measure the severity of depressive symptoms include the Hamilton Rating Scale for Depression (HAM-D, Hamilton 1960), the Montgomery-Asberg Depression Rating Scale (MADRS, Montgomery and Asberg 1979) and the Raskin Scale (Raskin 1988). Other observer-rated scales are used e.g. the Bech-Rafaelsen Melancholia Scale (MES, Bech et al. 1986) and the Newcastle Depression Diagnostic Scale (NDDS, Davidson et al. 1984) to measure the severity of melancholic states and the Bipolar Depression Rating Scale (Berk et al. 2007) to measure depression in bipolar disorder. Of the above mentioned observer-rated scales, the HAM-D is perhaps more commonly used than the others.

There are also measures having both self-report and clinician-administrated forms, these includes the Inventory of Depressive Symptomatology (IDS, Rush et al. 1996) and the Quick Inventory of Depressive Symptomatology (QIDS, Rush et al. 2003) derived from IDS. Both of these inventories are less dependent on somatic factors than HAM-D and are able to detect atypical and melancholic features of depression.

4.2.2.1.4 Beck Depression Inventory

The items of Beck Depression Inventory (BDI) were originally derived from observations of depressed patients during the course of psychoanalytic psychotherapy (Beck and Steer 2000). Beck proposed that the symptoms of depression could be explained in cognitive terms i.e. the biased interpretations of events were attributed to the activations of negative representations of the self, the personal world and the future (the negative cognitive triad) (Beck 2005).

The original 21-item version was published in 1961 (Beck et al. 1961), each item represented by four or five statements describing symptom severity from low to high and the subjects were asked to identify the statements that best described their feelings "at the present time/at the time of interview". Later eight new versions have been published, including an abbreviated version containing 13 items (Beck and Beck 1972); BDI-IA (Beck et al. 1979a) to eliminate duplicate severity descriptors, to reword certain items and to lengthen the time frame to the "last week, including today"; revised BDI-IA (Beck and Steer 1987) and new revised BDI-IA (Beck and Steer 1993) with new scoring; the Beck Depression Inventory-II (BDI-II, Beck et al. 1996) with a modification of items to reflect DSM-IV criteria (e.g.items covering increase in appetite, increase in sleep, agitation and psychomotor retardation), to simplify wording and to extend the time frame to 2 weeks, and BDI for Primary Care (BDI-PC) and Fast Screen (BDI-FS, Beck et al. 1997). In addition, many other versions exist, especially in non-English translations (Beck et al. 1988a), e.g. the Finnish modification of the short form of the Beck Depression Inventory measuring depression symptoms and self-esteem, called the Raitasalo's modification of the short form of BDI (RBDI, Raitasalo 2007). The correlation between the various forms and versions of the BDI has been found to be very high (Beck et al. 1988a).

Each of the BDI-IA item sets contains four statements, each describe symptom severity along an ordinal continuum from absent or mild (a score of 0) to severe (a score of 3). The item sets cover areas of sadness, pessimism, sense of failure, dissatisfaction, guilt, punishment, self-dislike, self-accusations, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, body image change, work difficulty, insomnia, fatiguability, loss of appetite, weight loss, somatic preoccupation and loss of libido. The manual of the new revised BDI-IA suggests the following interpretation of severity scores: 0-9, minimal;

10-16, mild; 17-29, moderate; and 30-63 severe depression, with the cut-off score of 15 for maximal efficiency to diagnose DSM-III-R mood disorder (Beck and Steer 1993). It has been also suggested that the cut-off point of 12/13 has the best predictive value to diagnose ICD-10 depressive disorder (Lasa et al. 2000).

The BDI shows high internal consistency, Cronbach's alphas ranged from 0.76-0.95 in clinical and from 0.73-0.90 in non-clinical populations (Beck et al. 1988a). Also the validity of BDI with other measures of depressive symptom severity has been high, as for psychiatric patients the mean correlations between the BDI and HAM-D has been found to be 0.73 and for non-psychiatric subjects from 0.73 to 0.80 (Beck et al. 1988a). BDI has shown a high short-term test-retest correlation (r=0.60-0.90) (Beck et al. 1988a), and also a fairly strong correlation with anxiety scales, e.g. with Beck Anxiety Inventory (r=0.61) (Beck et al. 2000).

4.2.2.1.5 Hamilton Rating Scale for Depression

The Hamilton Rating Scale for Depression (HAM-D) is an observer-rated depressive symptom rating scale to measure the severity of depressive symptoms in patients with primary depressive illness (Hamilton 1960). The quantification of symptom severity may be used to estimate symptom severity before treatment, gauge the effect of treatment on symptoms or detect a return of symptoms (e.g. relapse or recurrence) (Hamilton 2000). The original scale had 21 items with e.g. items of depersonalization and diurnal variation of the illness (Hamilton 2000). At least 20 published versions of the Hamilton depression scale have since been developed together with structured interview guides, self-report forms and computerized versions of the scale (Williams 2001). The 27-item (Gelenberg et al. 1990) and 29-item (Williams 1988) versions of the scale include also items for atypical depression. However, the 17-item version with its many modifications is the most commonly used, covering areas of depressed mood, feelings of guilt, suicide, insomnia (early, middle and late), work and activities, psychomotor retardation, agitation, anxiety (psychological and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis, loss of weight and insight. The HAM-D items are scored from 0 to 4 or 0 to 2. Items with quantifiable severity are scored 0 to 4; 4 indicates the greatest severity. Some symptoms are believed to be more difficult to quantify reliably, and these items have a range of 0 to 2. When compared with global measure of depression severity, scores over 23 indicated very severe, 19-22 severe, 14-18 moderate, 8-13 mild depression and 7 or under normal condition (Kearns et al. 1982). The internal consistency has been found to be higher (≥0.8) with the structured than with the unstructured interview (Potts et al. 1990). Correlations between the HAM-D and other clinician-rated instruments, including MADRS, range between 0.8 and 0.9 (Hamilton 2000). HAM-D gives more weight to somatic signs and symptoms than to cognitive symptoms (e.g. guilt), and the 17-item version does not include reverse neurovegetative symptoms (e.g. oversleeping and overeating) (Hamilton 2000). Recently its use as a golden standard for the assessment of depression has been questioned due to the possible flaws in its psychometric and

conceptual properties: many scale items have been found to be poor contributors to the measurement of depression severity or have poor interrater and retest reliability; the format for response options has been found not to be optimal and content validity to be poor (Bagby et al. 2004).

4.2.2.2 Epidemiology of symptoms of depression

The prevalence of depressive symptoms varies depending on the population studied and criterion used. In a summary of ten population surveys between 1957 and 1992, it was found that one tenth to one third of the subjects had suffered from depressive symptoms (Lehtinen and Joukamaa 1994). In another review of 36 studies of subthreshold depression, the prevalence of depressive symptoms varied from 2.2% to 24% in the community and epidemiological setting and from 5.4% to 15.6% in primary care setting, depending on the definition of the condition (Pincus et al. 1999).

The prevalence of depressive symptoms measured by BDI has been similar in different populations. In a sample of 298 adults from the US general population 80.3% of participants had BDI scores less than 10, 10.7% from 10 to 15, 5% from 16 to 23 and 4% over 23 (Oliver and Simmons 1984). In a Finnish study of 2018 adults from the general population 77% of subjects scored on the BDI below 10, 18% between 10 and 18, 4% between 19-29 and 1% above 30 (Honkalampi et al. 2000). Recently in a study among 937 Israeli adults 78.5 % of respondents scored less than 10, 13.2% from 10 to 15, 4.5% from 16 to 23 and 3.8% 24 or above (Iancu et al. 2003).

In the National Institute of Mental Health Epidemiological Catchment Area (ECA) study consisting of 18 571 subjects, 47% reported at least one and 23.1% at least two DSM-III criterion of depression in their lifetime, but not meeting the criteria for MDD and/or dysthymia (Johnson et al. 1992). In a subsample of 9 160 subjects from the ECA study, 19.6% of the general population reported one or more depressive symptoms in the previous month (1-month prevalence) and one-year prevalence of two or more depressive symptoms was 11.8% (Judd et al. 1994). In the National Comorbidity Survey, 10.0% of 8 098 respondents met the criteria for lifetime minor DSM-III-R depression (2 to 4 symptoms of MDD without a lifetime history of either MDD or dysthymia) (Kessler et al. 1997a) and in the Netherlands Mental Health Survey and Incidence Study (Cuijpers et al. 2007) 7.5% of 5 504 respondents met the criteria for minor DSM-IV depression in the previous year (2 to 4 symptoms of MDD, without a lifetime history of mood disorder).

4.2.2.3 Clinical impact of subthreshold symptoms of depression

Less severe constellation of depressive symptoms not meeting the criteria of MDD are often called subthreshold disorders, but also in a number of other ways, including minor depression and depressive symptoms threshold (Pincus et al. 1999). These categories have been defined in various ways, e.g. subthreshold depression in five, minor depression in nine and depressive symptom thresholds in three different ways (Pincus et al. 1999). In a

review of subthreshold mental disorders it was found that the minimum number of symptoms required for a diagnosis of one of the subthreshold conditions ranged usually from one to six, the most common minimum was two; the duration of the symptoms required for the subthreshold condition varied from none to two weeks, and out of 36 studies included in the review, 25 had not included impairment criterion, only 4 had ruled out lifetime mood disorder and 9 general medical condition (Pincus et al. 1999). Thus, the use of the title of subthreshold depression is diverse.

Although not meeting the diagnostic criteria of MDD, adults with subthreshold level of depressive symptoms have been reported to have more medical comorbidity (Coulehan et al. 1990), more days lost from work (Skodol et al. 1994; Judd et al. 1996), more mental health visits (Skodol et al. 1994), more suicide attempts (Johnson et al. 1992), poorer functional status (Wells et al. 1992; Judd et al. 1996; Olfson et al. 1996), poorer health status (Wells et al. 1992; Judd et al. 1996), more social irritability (Judd et al. 1996), more financial strain (Judd et al. 1996), more number of bed days (Wells et al. 1992), more days with pain (Wells et al. 1992) and worse outcome of various chronic diseases (Katon 2003) , including diabetes (Lin et al. 2004) and coronary disease (Ruo et al. 2003) than individuals without these symptoms. From ECA study, it has been estimated, based upon population attributable risk, which adjusts for prevalence, that there is as much or more service burden and impairment associated with depressive symptoms than with the formal mood disorders of major depression and/or dysthymia (Johnson et al. 1992).

4.2.2.4 Course and outcome of symptoms of depression

Subjects with depressive symptoms are a very heterogeneous group, including individuals with partially remitted or prodromal MDD, a transient adjustment to a stressful life-event, symptoms that are secondary to a general medical illness or a recurrent brief depressive condition (Olfson et al. 1996; Vuorilehto et al. 2005), thus the course and outcome of depressive symptoms depends on the population studied.

In a Zurich Cohort Study of 591 Young Adults during a 15-year follow-up approximately one third of the subjects with subthreshold depression (1-2/9 symptoms of DSM-IV MDD) developed MDD (Angst et al. 2000). In a Baltimore ECA study, during a 13-year follow-up, 10% of 1920 subjects with subthreshold depressive symptoms (3 or more symptoms of DSM-III-R MDD, but not meeting criteria of MDD) developed MDD, 5% dysthymia and 8% comorbid MDD and dysthymia (Chen et al. 2000). Among 4796 subjects in the Netherlands Mental Health Survey and Incidence study (NEMESIS), the risk of developing DSM-III-R MDD within 2 years was 1.8%, 4.0% and 8.0% in subjects without depressive symptoms, one key symptom only and minor depression (one key symptom and 1-3 other symptoms in 1 year), respectively (Cuijpers et al. 2004). During a 8-year follow-up among 1265 adolescents, subthreshold depression (depressed mood or loss of interest for 2 weeks, but not having 5 or more DSM-IV MDD symptoms or significant distress or impairment of functioning) at ages 17 to 18 years was associated with later depression and suicidal tendencies, prognosis being similar among sample members with subthreshold depression and major depressive

disorder (Fergusson et al. 2005). In their review of 23 studies, Cuijpers and Smit found that the incidence of MDD in subjects with clinically relevant depressive symptoms was larger than in subjects without such symptoms (Cuijpers and Smit 2004). Thus, although most individuals with depressive symptoms recover, a substantial proportion will develop MDD or dysthymia.

4.2.3 Major depressive disorder (MDD)

4.2.3.1 Diagnosis of MDD

There are currently two diagnostic classification systems in use, the DSM-IV (American Psychiatric Association 2000b) and ICD-10 (World Health Organization 1992, 1993; Tautiluokitus 1996). In Finland ICD-10 is used in clinical practice as an official classification, whereas DSM classification is usually applied in research programmes.

DSM-IV MDD is characterized by having one or more major depressive episodes (MDE's). Besides the required core symptom of persistent depressive mood or significant loss of interest or pleasure being present during the same two-week episode, there must be at least four of the following accompanied symptoms (total of five symptoms): significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate and recurrent thoughts of death, recurrent suicidal ideation or suicide attempt or specific plan for committing suicide. Moreover, the symptoms must cause clinically significant distress or impairment in social, occupational or other important areas of functioning and should not be due to the direct physiological effects of a substance or a general medical condition or bereavement. An episode of MDD may be classified as mild, moderate or severe, based on the number of symptoms, the severity of the symptoms and the degree of functional disability and distress (American Psychiatric Association 1987, 1994, 2000b).

The diagnosis of MDD in both DSM-IV and ICD-10 are almost compatible. However, ICD-10 includes also fatigue or loss of energy among the core symptoms, splits feelings of worthlessness and inappropriate guilt into two and requires one symptom less.

In this thesis, unless otherwise specified, depression refers to unipolar DSM-IV MDD.

4.2.3.2 Epidemiology of MDD

Major depressive disorder is a common disorder, widely distributed in the population. Several epidemiological studies have estimated the prevalence of depression in the general population around the world (Table 1.). Mood disorders are found to be the next common of mental disorders after anxiety disorders (Demyttenaere et al. 2004). It is estimated that during their lifetime, approximately 20% of the population will suffer an episode of MDD (Kessler et al. 1994). The lifetime risk for MDD is nearly twice as high for females as for males and is fairly low until early teens, when it begins to rise in roughly linear fashion (Kessler et al. 1994), the median age of onset being 30 years (Kessler et al. 2005a).

Table 1. Prevalence of MDD.

Lifetime prevalence of MDD					
NCS	17.1%	DSM III-R	(Kessler et al. 1994)	USA	N=8098
NCS-R	16.2%	DSM-IV	(Kessler et al. 2003)	USA	N=9282
NESARC	13.2%	DSM-IV	(Hasin et al. 2005)	USA	N=43093
NEMESIS	15.4%	DSM-III-R	(Bijl et al. 1998)	Netherlands	N=7076
ESEMeD	12.8%	DSM-IV	(Alonso et al. 2004)	Europe[a]	N=21425
12-month prevalence of MDD					
ECA	5.8%	DSM-III	(Regier et al. 1993)	USA	N=18572
NCS	10.3%	DSM-III-R	(Kessler et al. 1994)	USA	N=8098
NCS-R	6.6%	DSM-IV	(Kessler et al. 2003)	USA	N=9282
OHS	4.1%	DSM-III-R	(Offord et al. 1996)	Canada	N=9953
NESARC	5.3%	DSM-IV	(Hasin et al. 2005)	USA	N=43093
NEMESIS	5.8%	DSM-III-R	(Bijl et al. 1998)	Netherlands	N=7076
ESEMeD	3.9%	DSM-IV	(Alonso et al. 2004)	Europe[a]	N=21425
FINHCS	9.3%	DSM-III-R	(Lindeman et al. 2000)	Finland	N=5993
Health 2000	4.9%	DSM-IV	(Pirkola et al. 2005)	Finland	N=6005

[a] Belgium, France, Germany, Italy, Netherlands and Spain

In the Outcome of Depression International Network (ODIN) study in five European countries, an overall prevalence of ICD-10 and DSM-IV depressive disorders (MDD, dysthymia and adjustment disorders with depressive mood) was found to be 8.56% (Ayuso-Mateos et al. 2001). In a critical review of 27 studies of the size and burden of mental disorders in Europe, the estimated 12-month prevalence of MDD ranged from 3.1% to 10.1%, with the median being 6.9% (Wittchen and Jacobi 2005).

In the Mini Finland Health Survey of 8000 adults, the 1-month prevalence of neurotic depression using Present State Examination (PSE) interview was 4.6% (Lehtinen et al. 1990). The 6-month prevalence of DSM-III-R MDE in a computer assisted telephone interview study of 2293 Finnish adults using UM-CIDI Short Form was found to be 4.1% (Isometsä et al. 1997). The 12-month DSM-III-R prevalence of major depressive episode in a Finnish Health Care Survey (FINHCS) of 5993 Finnish adults using also UM-CIDI Short Form was found to be 9.3% (Lindeman et al. 2000), whereas in another recent Finnish study, the Health 2000, with 6005 adult participants, the 12-month prevalence of MDD using the German computerized version of the CIDI (M-CIDI) was reported to be 4.9% (Pirkola et al. 2005). The difference in these prevalences may be due to the methodological factors, such as different instruments, diagnostic criteria and sampling methods (e.g. in UM-CIDI Short Form unlike in M-CIDI, it is impossible to make differential diagnoses between unipolar, bipolar or schizoaffective mood disorders, residual schizophrenic disorders with superimposed MDE or organic mood disorders; the age range in FINHCS was wider than in Health 2000, 15-75 years and over 30 years, respectively; in Health 2000 MDD, not MDE diagnosis was used).

4.2.3.3 Aetiology of MDD

Major depressive disorder is a complex, multifactorial disorder, where the risk factors are seen to be related and interacting with each other (Kendler and Prescott 2006). An individual's probability of suffering an episode of MDD is affected by factors of several domains, including genetic risk factors (Levinson 2006), hormonal and neurobiological influences (Manji et al. 2001; Nestler et al. 2002), low birth weight (Costello et al. 2007), poor parenting (Parker 1979), parental depression (Lieb et al. 2002), childhood physical (Widom et al. 2007) or sexual (Kendler and Prescott 2006) abuse, childhood parental loss (Kessler et al. 1997b; Kendler and Prescott 2006), predisposing personality traits (Angst and Clayton 1986; Hirschfeld et al. 1989), early onset of an anxiety disorder (Kessler et al. 1996; Young et al. 2004), low social support (Kendler and Prescott 2006), marital difficulties (Whisman et al. 2000), history of MDD (Lewinsohn et al. 1988), prior depressive symptoms (Cuijpers and Smit 2004), substance abuse (Kessler et al. 1996), circadian abnormalities (Bunney and Bunney 2000) and stressful life-events (Paykel et al. 1969; Kendler and Prescott 2006). Temperamental factors together with genetic vulnerability and adverse life-events are likely to form one of the key domains of liability to major depression (Kendler and Prescott 2006).

4.2.3.3.1 Heritability of MDD

Major depression is a familial disorder and its familiality mostly results from genetic influences (Kendler and Prescott 2006). A meta-analysis of five studies found that first-degree relatives of individuals with MDD have a nearly threefold increased risk of developing MDD compared with control samples (Sullivan et al. 2000). The heritability or the proportion of variation due to genetic factors for MDD has been usually reported to be around 37% (Sullivan et al. 2000). These estimates are grounded mostly on community based twin studies, whereas on clinically based studies the heritability has been on the order of 70% (McGuffin et al. 2007). However, the heritability estimate of MDD in a community based twin study increased also to about 70%, when incorporating an index of severity, having data at two time points and incorporating measurement error in the model (Kendler et al. 1993a). Therefore, it has been recently concluded that the heritability of MDD might be as high as nearly 80% (McGuffin et al. 2007). Moreover, the heritability of MDD has been found to be greater in women than in men (Kendler et al. 2001), in a most recent study 42% and 29%, respectively (Kendler et al. 2006c).

Current genetic studies have been focused on two phenotypes: MDD and personality traits like neuroticism that predict increased risk for depression (Levinson 2006). The genes that predispose to depression are not necessarily the same for females and for males (Kendler et al. 2001) and it is likely that the genetic liability to MDD is contributed by multiple genes, each having a small effect e.g. 5-HT transporter gene (Zhou et al. 2005), glucocortcoid receptor gene (van Rossum et al. 2006), brain-derived neurotrophic factor gene (Kaufman et al. 2006), and their possible interactions (Kim et al. 2007). Other possible new candidate genes may be involved to newer hypotheses about the mechanisms of depression e.g. sleep, circadian rhythms and inflammation (Levinson 2006).

4.2.3.3.2. Childhood experiences and MDD

The risk for adult MDD has been significantly correlated with a history of having experienced poor parenting (Kendler and Prescott 2006). Among female twins the lifetime risk for MDD, and also for other internalizing disorders, is associated with coldness and authoritarianism of both mothers and fathers and overprotectiveness of mothers, e.g. moving from an average level of maternal coldness, measured by the Parental Bonding Instrument (Parker et al. 1979), to 1 sd above the mean, increased the lifetime risk for depression by above 30% (Kendler and Prescott 2006). In their study of what aspects of parenting received in childhood were associated with adult major depression, Kendler and Prescott found no evidence of shared family environment affecting the risk for MDD; instead it was hypothesized that poor parenting increased the risk for MDD through individual specific environment i.e. individuals may react to parenting in different ways guided in part by genetically influenced characteristics e.g. temperament (Kendler and Prescott 2006).

Other childhood experiences including parental loss and childhood sexual abuse, have also been found to increase the risk for MDD and other adult psychopathology, parental death increasing specifically the risk of adult MDD (Kendler and Prescott 2006).

The childhood adversities increasing the risk for adult depressiveness have been found to be partly mediated by adult risk factors, supporting a pathway hypothesis from childhood adversities to depressiveness through adult risk factors (Korkeila et al. 2005). Evidence has also been found to support the vulnerability hypothesis i.e. the consequences of an unfavourable childhood background might be worse if combined with adult adverse life-events (Korkeila et al. 2005). Futhermore childhood adverse life-events have been found to associate with adult depression-prone personality characteristics (Korkeila et al. 2004).

4.2.3.3.3 Adult adverse life-events, social support and MDD

Adult adverse life experiences and poor social support have been found to associate with depression (Paykel et al. 1969; Brown and Harris 1978). In their study among female twins, Kendler and Prescott (2006) found that 13/15 categories of stressful life-events (SLE) were associated with an increased risk of major depression, including personal events (assault, major financial problems, serious housing problems, job loss, serious difficulties at work, serious illness, serious marital problems, divorce/separation, loss of confidant), network events (interpersonal conflict with an individual in the network, crisis experienced by someone in the network, illness or death of someone in the network), but not robbery or legal problems. Men were more likely to have depressive episodes following divorce, separation and work difficulties, whereas women were more sensitive to events in their proximal social network events (Kendler and Prescott 2006). Most of the events were associated with an increase of 2 to 7 times the baseline risk, the highest being observed for the rarest event, assault, which had an OR of 17.9 for MDD. The risk for major depression increased further if the number or severity of events increased. Of four psychological dimensions of life-events (entrapment, danger, loss and humiliation), high ratings of loss and humiliation were associated with increased risk for depression among individuals with high-threat events (Hazard ratios 1.70 and 1.45, respectively) and the combination of high ratings of humiliation and loss created the highest risk for depression (Kendler and Prescott 2006).

Low social support (combined measure of social integration, emotional support and instrumental support) has also been found to increase the risk for developing future episodes of major depression, even after controlling for the history of past depressive episodes (Kendler and Prescott 2006).

In VDS, 91% of the patients reported life-events, on average 4.1±3.0 events per preceding year. Although life-events were distributed evenly between the time preceding depression, the prodromal phase, and the index MDE, 76% of the patients attributed their depression to some event (Leskelä et al. 2004).

Recent findings support bidirectional models of person environment interrelationships. Not only can the causal relationship between environmental adversity and an individual be from environment to person, but also from person to environment (Kendler and Baker 2007). Individual differences in personality, which result partly from genetic influences, have been found to impact on the way in which humans structure the world around them, and to make them more or less likely to experience stressful life-events and to have poor quality interpersonal relationships, which in turn 'feed back' to them, influencing their risk for subsequent psychiatric illness (Kendler et al. 2003b).

Consistent with diathesis-stress theories of depression that hypothesized life stress being an important component in the aetiology of depression, but requiring also other vulnerability factors to explain onset conditions (Monroe and Hadjiyannakis 2002), several gene-by-environment interactions have been reported. In gene-environment interaction the genetic risk influences the overall liability to illness and alters the individual's sensitivity to the pathogenic effects of the environment (Kendler and Prescott 2006). Caspi et al. (2003) reported that individuals with one or two short allele of the 5-HTT promoter polymorphism, showed more depressive symptoms, diagnosable depression and suicidality in relation to stressful life-events or childhood abuse than individuals homozygous for the long allele. Since that, the result of the genetic mediation by 5-HTTLPR of vulnerability to adverse environment has been replicated at least by fifteen studies, whereas not at least by two, possibly due to the sample age composition, selected samples or use of unreliable measures of environment (Uher and McGuffin 2007). Also other gene-environment interactions have been reported e.g. serotonin receptor 2A gene may be involved in the development of depression by influencing the ability of individuals to use environmental support (Jokela et al. 2007) and dopamine transporter gene, genotype A2/A2, may be involved in the development of depressive symptoms in individuals with adverse life-events (Elovainio et al. 2007). Other possible interactions are e.g. an interaction between life-events and neuroticism, where neuroticism has a greater impact on the risk of MDD at high rather than low levels of stressful life-events (Kendler et al. 2004).

4.2.3.3.4 Integrative models for MDD

Attempts to create intergrative models for the risk factors for MDD have been made e.g. in Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD) for both women and for men (Kendler and Prescott 2006). These models predicted depressive episodes in the year before the most recent interview. Eighteen risk factors were organized into five developmental tiers reflecting childhood (genetic risk factors, disturbed family environment, childhood sexual abuse, childhood parental loss), early adolescence

(neuroticism, low self-esteem, early-onset anxiety, conduct disorder), late adolescence (low educational attainment, lifetime traumas, low social support, substance misuse), adulthood (divorce, history of MDD) and the preceding year (marital problems, total difficulties of severe life-events). The final model for women and men accounted for 52.1% and 48.7%, respectively, of the variance in liability to develop an episode of MDD. For both female and male, the overall result suggested that there would be three broad patterns of risk factors to MDD characterized by internalizing and externalizing symptoms and adversity/interpersonal difficulties and their cross-influences. Low self-esteem and childhood parental loss were more potent variables in the model for men than in women. The results suggested that, from an aetiological perspective, MDD is largely the same disorder in men and in women.

4.2.3.4 Pathogenesis of MDD

The pathogenesis of MDD is not known precisely, however there are several hypotheses. The monoamine hypothesis proposes that mood disorders are caused by a deficiency in serotonin or noradrenaline systems (Thase et al. 2002). However, it has been found that in its original form the hypothesis is inadequate, therefore the hypothesis has evolved to include e.g. adaptive changes in receptors to explain the delay in onset of the antidepressant effect (Hirschfeld 2000). Moreover, monoamine depletion studies have demonstrated decreased mood in subjects with a family history of MDD and in drug-free patients with MDD in remission, but not in healthy subjects, and thus failed to demonstrate a causal relation between dysfunction in the monoamine systems of serotonin and noradrenalin and MDD (Ruhe et al. 2007). More recently the hypothesis has evolved into the direction of a chemical or molecular hypothesis of depression, which presumes that mood disorders are produced by long-term changes in the production or activity of molecules e.g. neuropeptides, growth factors and their receptors and intracellular signalling molecules in the brain (Manji et al. 2001; Castren 2005).

Stress promotes adaptation, but a perturbed diurnal rhythm or failed shut-off of mediators e.g. glucocorticoids and growth hormone, after stress leads over time to allostatic load (wear and tear on the body) (McEwen 2003). Abnormal, excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis is observed in approximately half of individuals with depression (Nestler et al. 2002). It has been suggested that not only the overall production of cortisol, but also enhanced corticotrophin releasing factor (CRF) carry the responsibility for HPA-axis hyperactivity (Nestler et al. 2002). In addition to directly causing neuronal atrophy and hippocampal volume reduction, life stress and glucocorticoids also reduce cellular resilience and neurogenesis (Sapolsky 2000; Manji et al. 2001). The excessive amount of glucocorticoids may also be partly responsible for the decreased level of brain-derived neurotrophic factor (BDNF) and thus the deficiency in neutotrophic support (Nestler et al. 2002). It has also been suggested that the elevation of amygdala activity caused by depressive illness may be the first step that leads to overactivation of systems involved in physiologic and behavioural coping (McEwen 2003).

The brain-derived neurotrophic factor hypothesis of depression postulates that loss of BDNF is directly involved in the pathophysiology of depression, and its restoration may underlie the therapeutic efficacy of antidepressant treatment. However, critical views have been recently presented for reassessing this hypothesis and suggested that maybe the role of BDNF lies more in the genesis of depressive symptoms than at the core of disease pathology (Groves 2007).

Many brain regions have been implicated in regulating emotions and thus also postulated to mediate the symptoms of depression (Nestler et al. 2002). Magnetic resonance imaging (MRI) studies have demonstrated that small hippocampal volumes associate with recurrent MDD, and when compared with control subjects, MDD patients have had smaller volumes of the orbital frontal cortex and anterior cingulated cortex (Videbech and Ravnkilde 2004; Campbell and MacQueen 2006). MRI studies have also revealed decreased white matter volumes in the left anterior cingulated gyrus and right middle frontal gyrus among elderly MDD patients (Bell-McGinty et al. 2002), whereas patients with familial MDD have shown enlarged middle genu area of corpus callosum (Lacerda et al. 2005). Increased rate of white matter hyperintensities, possily implicating impairment of white matter tracts connecting the cortex with the limbic areas, has been constantly found in frontal lobes and basal ganglia in elderly MDD patients (Videbech 1997; MacFall et al. 2001). Recently, white matter abnormalities have been revealed also in first-episode, treatment-naïve young adults in frontal, temporal and parietal lobes with a modern MRI technique, diffusion tensor imaging (DTI) (Ma et al. 2007). Functional neuroimaging techniques i.e. functional magnetic resonance spectroscopy (fMRI), positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) have shown changes among MDD patients in several brain areas, including regions of orbital and medial prefrontal cortex, the amygdala and related parts of the striatum and thalamus (Drevets 2000). Different brain regions probably correlate with discrete symptom domains of major depression and together compose the overall syndrome of MDD (Milak et al. 2005).

Most recently the network hypothesis has proposed that problems in information processing within neural networks, rather than changes in chemical balance, might underlie depression, and that antidepressant drugs induce plastic changes in neuronal connectivity e.g. by increasing the expression and signalling of BDNF, which gradually lead to improvements in neuronal information processing and recovery of mood (Castren 2005).

4.2.3.5 Course and outcome of MDD

It has been stated that the optimal outcome of treatment of MDD would be remission with an absence of both symptoms and functional impairments for at least 4 weeks, however this definition is not yet universally accepted (Keller 2003).

The results of several epidemiological (Eaton et al. 1997; Spijker et al. 2002; Kessler et al. 2003; Hämäläinen et al. 2004) and clinical studies (Solomon et al. 1997; Furukawa et al. 2000; Kennedy et al. 2003; Holma et al. 2007) evaluating the duration of MDE have

varied depending on the methodology used and population concerned. The median duration of MDE in the ECA (Eaton et al. 1997), the NEMESIS (Spijker et al. 2002) and the Finnish Health Care Survey (Hämäläinen et al. 2004) study was 8-12 weeks, 3 months and 5 weeks, respectively. In the NCS-R study (Kessler et al. 2003) the mean duration of MDE was 16 weeks. In recent studies in clinical settings the median duration of MDE has been 3 months (Furukawa et al. 2000), 20 weeks (Solomon et al. 1997), 7 months (Kennedy et al. 2003) and 11 months (Holma et al. 2007). Overall, in clinical settings the duration of MDE seems to be somewhat longer than in epidemiological general population studies. Factors associated with MDE, such as number of prior episodes, longer pretreatment duration, severity and comorbid psychiatric disorders have been found to predict non-recovery or longer time to remission (Melartin et al. 2004).

Major depressive disorder appers to be a chronic illness, with high rates of recurrences and chronicity, but is also variable. Factors like, the severity of MDD and comorbidity, especially social phobia, have been found to predict the probability of, shorter time to and number of recurrences over a 5-year follow-up (Holma et al. 2007). In a prospective 12-year National Institute of Mental Health Collaborative Depression Study, patients were symptomatically ill 59% of weeks and the symptom severity commonly alternated over time in the same patient (Judd et al. 1998). Approximately 80% of individuals who have experienced MDE will have at least one more episode of MDD during their lifetime (Angst 1986; Mueller et al. 1996) and a chronic course of MDE lasting over two years will have about 20% and over 5 years 12 % (Keller et al. 1992). More recently, over the 5-year follow-up in VDS, 29.3% had no recurrences, whereas 30.0% experienced one, 12.9 % experienced two and 27.9% experienced three or more recurrences (Holma et al. 2007).

An increased rate of suicidal ideation, suicide attempt and completed suicide is associated with MDD. In a recent meta-analysis of completed suicides, 43.2% of victims had an affective disorder, the risk of having a depressive disorder was higher in females than in males (Arsenault-Lapierre et al. 2004). In the Finnish psychological autopsy study of completed suicides during one year, 59% of victims had depressive disorder (Henriksson et al. 1993). The prevalence of suicidal ideation ranges from 47% to 69% in patients with MDD (Asnis et al. 1993; Bronisch and Wittchen 1994; Zisook et al. 1994), the estimated risk of a non-fatal suicide attempt after the first lifetime episode of MDD is about 40% (Malone et al. 1995) and an inpatient with MDD has about a 20-fold risk of completed suicide (Harris and Barraclough 1997). In a recent Finnish study almost 60% of the depressed secondary-level care psychiatric out- and inpatients reported suicidal ideation, 15% attempted suicide at the baseline and 8% during the 18-month follow-up period (Sokero 2006).

4.2.3.6 Comorbidity of MDD

The term comorbidity is used to indicate the occurrence of two or more distinct disorders in a person in a defined period of time (Klerman 1990). The concept of comorbidity has its origin in general medicine (Feinstein 1970), but has also been increasingly applied in

psychiatry not only to indicate the co-occurence of psychiatric and a general medical diagnosis (Stordal et al. 2003), but also of two or more psychiatric diagnoses (Melartin et al. 2002; Kessler et al. 2005b). In psychiatry the concept of comorbidity has been supported by DSM-III (American Psychiatric Association 1980) and DSM-IV (American Psychiatric Association 1994) with a multiaxial classification system. Recently the concept of comorbidity has been criticized for being perhaps an artefact produced by the categorical diagnostic classification system (Maj 2005) and arguments for a dimensional approach has been made (Korszun et al. 2004; Watson 2005).

There is increasing evidence of the clinical significance of comorbidity including treatment response and overall clinical outcome. Comorbidity has been found to be one of the major factors associated with poor outcome of MDD by increasing the risk of relapse or recurrence (Alnaes and Torgersen 1997), chronicity (Mueller et al. 1994), suicide (Hansen et al. 2003), residual symptoms (Paykel et al. 1995) and psychosocial impairment (Rytsälä et al. 2005). However, several factors may influence the comorbidity findings, including assessment method used for diagnosis, the time frame of assessment for each disorder (e.g. lifetime or current) and overall study design (Wittchen 1996).

4.2.3.6.1 MDD and axis I comorbidity

Comorbid psychiatric disorders are common among individuals with MDD in general population (Kessler et al. 1996; 2003; Hasin et al. 2005), in psychiatric setting (Melartin et al. 2002) and also in primary care (Vuorilehto et al. 2005) studies.

Several general population studies have evaluated the prevalence of comorbid disorders among individuals with MDD. In NCS-R study (Kessler et al. 2003), about 80% of respondents with 12-month DSM-IV MDD had at least one axis I comorbid disorder, anxiety disorders being the most common (67.8%), followed by substance use disorder (27.1%). In NESARC study (Hasin et al. 2005) with lifetime DSM-IV MDD the most common comorbid axis I disorder was any anxiety disorder (41.4%), followed by any alcohol use disorder (40.3%). In a Finnish Health 2000 study, 32% of respondents with 12-month DSM-IV MDD had at least one comorbid disorder, anxiety disorder being the most common (25%), followed by alcohol use disorder (9%) (Pirkola et al. 2005). Regarding lifetime comorbidity, there is evidence that an anxiety disorder is significantly more likely to precede MDD than the reverse (Merikangas et al. 2003).

Comorbid disorders tend to be more common in clinical than in epidemiological studies, probably due to more serious course of illness associated with patients in clinical settings (Kessler et al. 1994). In a review of current axis I comorbidity of MDD patients in psychiatric settings, the reported prevalence of comorbid disorders varied widely: all in all, about half of the patients had a current anxiety disorder and about one fifth a current substance use disorder (Melartin et al. 2002). In VDS with current MDD about 70% of cases had at least one current axis I comorbid disorder, anxiety disorders being the most common, 57%, and substance use disorder the second common, 25% (Melartin et al.

2002). In a recent study (Rush et al. 2005) of 1376 outpatienst with DSM-IV MDD assessing the concurrent comorbidity of MDD with Psychiatric Diagnostic Screening Questionnaire, 61.8% of cases had at least one comorbid disorder, social anxiety disorder (20.8%) being the most common, followed by GAD (18.8%), OCD (13.4%), PTSD (12.4%), bulimia (11.9%), any alcohol use disorder (11.9%), panic disorder (11.1%) and agoraphobia (9.4%).

There are only a few studies of psychiatric comorbidity among primary care patients. MDD patients in primary care or psychiatric out-patient settings have not been found to differ markedly in current axis I comorbidity (Vuorilehto et al. 2007). In Primary Care-VDS (PC-VDS) of 137 patients with DSM-IV MDD, 59% had at least one current comorbid axis I disorder, any anxiety disorder being the most common, 50% (GAD 20%, social phobia 16%, panic disorder 9% and simple phobia 9%), followed by substance use disorder (16%) and somatoform disorder (14%) (Vuorilehto et al. 2005).

4.2.3.6.2 MDD and axis II comorbidity

By definition, personality traits defining personality disorders must be distinguished from characteristics that emerge in response to depression (American Psychiatric Association 2000b), which makes the assessment of comorbidity of MDD and personality disorders difficult, especially in cross sectional studies, during a major depressive episode.

There is only a little information of the prevalence of MDD with comorbid axis II disorders in the general population. In ODIN study (Casey et al. 2004), conducted in five European countries, and in NESARC study (Hasin et al. 2005), 22% and 38% of individuals, respectively, with MDD had personality disorder. The most common comorbid personality disorders in ODIN study were cluster C personality disorders, whereas in NESARC study obsessive-compulsive personality disorder (18.3%), followed by paranoid (15.1%), schizoid (10.2%), avoidant (9.6%), antisocial (8.1%), histrionic (5.3%) and dependent (2.2%) personality disorders (borderline, schizotypal and narcissistic were not included in the study).

In a review of current axis II comorbidity of MDD patients in psychiatric settings, the reported prevalence of comorbid personality disorders varied widely (18%-86%): overall, about half of the patients had a current personality disorder (Melartin et al. 2002). In a study of 859 out-patients, 51.3% with a current DSM-IV MDD had at least one personality disorder, cluster C disorders being the most common (27.3%), especially avoidant personality disorder (20.3%), followed by cluster B (14.1%) and cluster A (7.3%) personality disorders (Zimmerman et al. 2005). In VDS, 44% of patients with current MDD had at least one personality disorder, cluster C personality disorders being the most common (32%), followed by cluster A (19%) and B (14%) personality disorders (Melartin et al. 2002).

MDD patients appear to differ little in axis II comorbidity between primary care and psychiatric out-patient settings. Comorbid personality disorders have been found to be present in about half of MDD patients in primary care or psychiatric out- or inpatient settings, although the clusters might be unevenly distributed; cluster A personality disorders have been found to associate more with psychiatric care, whereas cluster B disorders more with primary care treatment (Vuorilehto et al. 2007). In PC-VDS, 58% of DSM-IV MDD patients had a comorbid axis II disorder, cluster B (35%) and C (35%) personality disorders being the most common, followed by cluster A (7%) personality disorder (Vuorilehto et al. 2005).

There are some studies of the long-term stability of personality disorders. In a study of 142 outpatients with MDD, the 10-year stability of categorical personality disorder diagnosis was found to be relatively poor and not higher than that of anxiety disorders (Durbin and Klein 2006). However, the relative stability of personality disorder dimensional scores was greater than that for categorical diagnosis, generally reaching a moderate level, and approached the long-term stability of normal-range personality traits.

4.2.3.7 Treatment of MDD

In order to improve the detection and treatment of MDD, several sets of evidence-based treatment guidelines have been published during the last decade. These guidelines cover the basics and objectives for the management of depression with various regimes, including pharmacotherapy, psychotherapy, combination of pharmaco- and psychotherapy, electroconvulsive therapy (ECT) and bright light therapy (Schulberg et al. 1998; Crismon et al. 1999; American Psychiatric Association 2000a; Anderson et al. 2000; Suomen Psykiatriyhdistys 2000; Bauer et al. 2002a, b; National Institute of Clinical Excellence 2004). Other treatments that have been used for MDD are among others exercise (Ernst et al. 2006) and sleep deprivation (Wirz-Justice 2006). New treatments for MDD currently being evaluated include brain stimulation (transcranial magnetic stimulation, deep brain stimulation and vagus nerve stimulation) (Eitan and Lerer 2006; Ressler and Mayberg 2007) and intravenous injection of ketamine (Zarate et al. 2006). Other targets for future agents include neuropeptide Y, vasopressin V1b, nicotinic cholinergic, delta-opiate, dopamine D1, cytokine, and corticotrophin-releasing factor 1 receptors, as well as, GABA, intracellular messenger systems, and transcription, neuroprotective and neurogenic factors (Manji et al. 2003; Mann 2005).

There are three phases of treatment: the acute, continuation and maintenance phases. In the acute phase, the aim of the treatment is full remission, in the continuation phase, the prevention of relapse, and in the maintenance phase, the prevention of recurrence (Suomen Psykiatriyhdistys 2000). The most used treatments for MDD in Finland are antidepressant treatment with or without augmenting and adjunctive medications; psychotherapy and ECT.

4.2.3.7.1 Antidepressant treatment

The more severe the depression is, the more important the antidepressants are for the treatment of MDD. In severe or psychotic depression antidepressant treatment is always indicated, whereas in mild or moderate cases of depression, effective psychotherapy, alone or combined with pharmacotherapy, are also possible alternatives (Suomen Psykiatriyhdistys 2000). Since most antidepressants have similar effectiveness, the choice of medication depends on the history of responses to medication, medication tolerability, adverse effects and likelihood of adherence, concurrent with other medical conditions and drug therapies and also cost of medication (Suomen Psykiatriyhdistys 2000). The decision to increase the dose, change the medication, or add another medication or therapy should be made, if there is not a clear response after 6 to 8 weeks treatment with the initial medication with adequate dose (Suomen Psykiatriyhdistys 2000), although recently stricter time limits of 3 to 4 weeks have been suggested (Trivedi et al. 2007). In a recent STAR-D study (National Institute of Mental Health) of 2876 out-patients, 37% remitted after the first antidepressant, 50% after two treatment steps and the theoretical cumulative remission rate after four active treatment steps during 8 months was 67% (Rush et al. 2006). An association between treatment response and marker alleles of both the GRIK4 (Paddock et al. 2007) and 5-HTR2A (McMahon et al. 2006) has been detected, indicating that the individual variation in antidepressant treatment outcome seems to have at least partial genetic basis. Altogether about 2/3 of those MDD patients who use antidepressant medication will respond and about half will be nearly symptom free after 6 to 8 weeks treatment (Suomen Psykiatriyhdistys 2000).

The continuation phase should generally last four to nine months after the induction of remission in order to prevent relapses, and after that, maintenance phase treatment should be considered after 3 or more lifetime episodes to prevent recurrences (Suomen Psykiatriyhdistys 2000). The factors that influence on the decision whether to use maintenance phase treatment include severity of the episodes (presence of suicidality, severe functional impairments and psychotic features), the risk of recurrence (residual symptoms between episodes, presence of comorbid conditions and number of prior episodes), possible side effects and patient preference (American Psychiatric Association 2000a).

4.2.3.7.2 Psychosocial treatment

Psychosocial treatment consists of specific psychotherapy and social support. This treatment should be considered regularly when substantial psychosocial stressors, interpersonal difficulties, or coexisting developmental or personality disorders are present (American Psychiatric Association 2000a). Specific psychotherapies that are used in the treatment of MDD include cognitive and cognitive-behavioural therapy, interpersonal psychotherapy, brief psychodynamic psychotherapy and certain problem-solving therapies (Roth and Fonagy 2005). In the acute phase treatment of mild or moderate depression, psychotherapy can be used alone or in combination with antidepressants. In the continuation and maintenance phase treatment, psychotherapy alone or in combination with antidepressants may reduce the risk of a relapse or recurrence (Suomen Psykiatriyhdistys 2000).

4.2.3.7.3 Electroconvulsive treatment (ECT)

Electroconvulsive treatment was developed 70 years ago and since then it has been used as a treatment for mental disorders. It has been found to be effective treatment for severe and psychotic depression and should be considered for MDD patients who have medication resistance or when rapid relief of depressive symptoms is needed e.g. severe suicidality (Suomen Psykiatriyhdistys 2000). In a recent review and meta-analysis on the efficacy of ECT, it was concluded that ECT is an effective short-term treatment for depression, and is probably more effective than drug therapy; bilateral ECT being moderately more effective than unilateral, and high dose ECT more effective than low dose (The UK ECT review group 2006).

4.3 Anxiety as a dimensional concept

4.3.1 Anxiety as an emotion

Feelings of fear and mild anxiety appear in everyday life. As an affect, anxiety is usually self-limited and does not significantly interfere with a person's functional capacity. Anxiety is often considered as a secondary emotion in response to the primary emotion of fear (Belzung and Philippot 2007). A prerequisite for the feeling of anxiety is thought to be the ability to keep in mind and to summon up prior emotional responses through the frontal cortex (Belzung and Philippot 2007). Also other brain regions including amygdala have been found to have a critical role in the processing of fearful and anxious stimuli (Stein et al. 2007). Moreover, it has been found that the individual variation in response to emotional stimuli is partly moderated by genetic factors e.g. the amygdala response to emotional face processing by functional variation in the serotonin transporter gene (Hariri et al. 2002).

4.3.2 Symptoms of anxiety

Not only depression, but also anxiety can be understood on a continuous scale, ranging from no anxiety symptoms, anxiety symptoms, subthreshold anxiety disorder and finally anxiety disorder. When enough signs and symptoms are clustered together, a diagnosis of anxiety disorder can be made. There seems to be also fluctuations across threshold and subthreshold levels over time among those who experience anxiety (Merikangas et al. 2003).

4.3.2.1 Measures of symptoms of anxiety

Anxiety symptoms can be measured by using general measures i.e. diagnostic interviews, general psychiatric symptoms measures and disorder specific scales. Diagnostic interviews applied to measure not only depression, but also anxiety symptoms are presented in 4.2.2.1.1., wheras general psychiatric symptoms measures applied to measure not only depression, but also anxiety symptoms are presented in 4.2.2.1.2.

4.3.2.1.1 Specific anxiety symptoms measures

Of anxiety disorder measures, only few assess general anxiety, including 21-item Beck Anxiety Inventory (BAI, Beck et al. 1988b) and the 14-item Hamilton Anxiety Rating Scale (HARS, Hamilton 1959). However, there are several scales developed to detect the symptoms of a specific anxiety disorder, including the Fear Questionnaire (FQ, Marks and Mathews 1979) for common phobia symptoms; the Anxiety Sensitivity Index (ASI, Reiss et al. 1986) and the Panic Disorder Severity Scale (PDSS, Shear et al. 1997) for panic disorder symptoms; the Mobility Inventory (MI, Chambless et al. 1985) for agoraphobia symptoms; the Social Phobia and Anxiety Inventory (SPAI, Turner et al. 1989), the Brief Social Phobia Scale (BSPS, Davidson et al. 1991) and the Liebowitz Social Anxiety Scale (LSAS, Liebowitz 1987) for social phobia symptoms; the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS, Goodman et al. 1989b; Goodman et al. 1989a) and the Padua Inventory (PI, Sanavio 1988) for obsessive-compulsive symptoms; the Clinician-Administered PTSD Scale (CAPS, Blake et al. 1990), the Impact of Event Scale (IES, Horowitz et al. 1979), the Post-traumatic Stress Diagnostic Scale (PDS, Foa et al. 1997) and the Mississippi Scale (MSS, Keane et al. 1988) for post-traumatic stress disorder symptoms and the Penn State Worry Questionnaire (PSWQ, Meyer et al. 1990) for the symptoms of pathological worry.

4.3.2.1.2 Beck Anxiety Inventory

The self-report Beck Anxiety Inventory was specifically developed as a measure to discriminate between anxiety and depression, although the correlation between BAI and e.g. BDI is substantial (r=0.61) (Beck et al. 2000). The BAI is well suited for monitoring change with treatment and may be a useful screening tool for unselected individuals (Beck et al. 2000). Each item in the scale is rated from 0 to 3, the total score ranges from 0 to 63. The recent guidelines suggest the following interpretation of severity scores: 0-9, normal; 10-18, mild to moderate; 19-29, moderate to severe and 30-63 severe anxiety (Beck et al. 2000). The BAI has high internal consistency (Cronbach's alphas reported in five studies ranged from 0.9 to 0.94) and has demonstrated moderate to high correlations with other scales e.g. with HARS (r=0.51) (Beck et al. 2000). BAI does not assess avoidance symptoms nor symptoms of generalized anxiety disorder (GAD), including worry, difficulty to concentrate, irritability or sleep disturbance (Beck et al. 2000).

4.3.2.2 Epidemiology of symptoms of anxiety

The symptoms of anxiety are common. In a primary care study with 1 001 patients, subthreshold symptoms of anxiety were as or more common than their respective DSM-IV axis I disorders: panic (10.5% vs. 4.8%), anxiety (6.6% vs. 3.7%), obsessive-compulsive (5.8% vs. 1.4%) (Olfson et al. 1996). Of general population studies, in the Epidemiological Catchment Area Program study (1980) and the Midlife development in the United States Survey (1996) the lifetime prevalence for panic attacks was found to be 5.3% and 12.7%, respectively (Goodwin 2003). In a Canadian community survey (1996) of social phobia, 39.6% of 1956 respondents had at least one, and most (27.8%) 1-3 out of 12 different DSM-IV social fears or avoidance during the last year; with the fear of eating while being observed being the least common (4.2%), and the fear of giving a speech in public the most common (15.1%) (Stein et al. 2000). In a French study of social phobia, 67.1% of 12 873 respondents from the general population had at least one strong fear in social situations and 26.9% of respondents fear or avoidance most or some of the time during their whole lifetime (Pelissolo et al. 2000). In a German study of generalized anxiety disorder, 7.8% and 4.1% of 4181 respondents from the general population reported a period of at least one month and 3 months in the past 12 months, respectively, when they felt themselves most of the time worried, tense or anxious (Carter et al. 2001). In a more recent study of obsessive-compulsive spectrum disorders among 591 young adults, the one-year prevalence for OCD, Obsessive-Compulsive Syndrome (1 symptom criteria and moderate distress) and obsessive-compulsive symptoms was 0.7%, 2,5% and 3.9%, respectively (Angst et al. 2004). Thus, the prevalences of anxiety symptoms and subthreshold anxiety disorders tend to be higher than the prevalence of a corresponding anxiety disorder.

Comorbidity between subthreshold conditions and between subthreshold and threshold conditions is common. In a 15-year longitudinal study of 591 general population young adults, 25% had subthreshold anxiety at least once during the five interviews, and of those, in at least one interview 32% had also subthreshold depression and 22% DSM-III-R MDD (Angst et al. 1997) In a more recent study of 1704 randomly selected adolescents, 16.5% had subthreshold anxiety and of those 38.3% had also subthreshold depression and 25.9% DSM-III-R MDD (Lewinsohn et al. 2004).

The prevalence of anxiety symptoms can be measured also by using symptom scales e.g. BAI. In such an Australian study among 326 students, 42% had BAI scores less than 9, 35% scored from 10 to 18, 17% from 19 to 29 and 6% over 30 (Creamer et al. 1995).

4.3.2.3 Clinical impact of subthreshold symptoms of anxiety

Less severe constellation of anxiety symptoms not meeting the criteria of any anxiety disorder, are often called subthreshold disorders, analogous to subthreshold depressive disorders (Pincus et al. 1999). Compared to subthreshold depressive disorders, subthreshold level of anxiety disorders are less studied and the information of these conditions is more sparse (Olfson et al. 1996; Magruder and Calderone 2000).

An increased rate of impairment and disability has been found to associate with subthreshold symptoms of anxiety. In a study of 201 primary care patients with subthreshold level of anxiety, Ormel et al. (1993) found that 40% of patients had at least mild impairment in their social, and 30% in their occupational role. Moreover, among patients with subthreshold level of comorbid anxiety and depressive symptoms, 43% had at least mild impairment in their social role, and 57% in their occupational role. In addition, anxiety symptoms with comorbid depressive symptoms have been found to associate strongly with functional somatic symptoms (Haug et al. 2004).

4.3.2.4 Course and outcome of symptoms of anxiety

Anxiety symptoms with or without comorbid depressive symptoms tend to be persistent and long lasting. In a study of 201 primary care patients, during 3½-year follow-up, only 29% of those who had baseline subthreshold symptoms of anxiety recovered fully and 36% of those who had baseline subthershold comorbid symptoms of depression and anxiety recovered fully (Ormel et al. 1993). In another 20-year longitudinal study 77 out of 591 young adults had obsessive-compulsive symptoms, but not OCD; of those 77 the course of obsessive-compulsive symptoms was chronic for 50%, recurrent for 35.7% and only 14.3% had a single episode (Angst et al. 2004).

There is indication, that the emergence of subthreshold or threshold depressive states among those with subthreshold or threshold anxiety states is far more common than the converse (Merikangas et al. 2003). In a 15-year longitudinal study of 591 young adults, anxiety states tended to develop either into depression alone or into anxiety with depression, whereas depression tended to be more stable than anxiety alone over time, the patterns of stability were similar also for subthreshold states (Merikangas et al. 2003).

4.3.3 Anxiety disorders

Anxiety disorders are among the most prevalent psychological disorders and also the burden of illness associated with these disorders is often considerable. Persons having anxiety disorder tend to have a high degree of comorbid conditions, especially depression, impairment, health care visits and disability (Fehm et al. 2005; Goodwin et al. 2005; Lieb et al. 2005).

Most common anxiety disorders included in DSM-IV and also discussed later are Agoraphobia, Panic Disorder Without Agoraphobia, Panic Disorder With Agoraphobia, Social Phobia, Specific Phobia, Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD) and Post-traumatic Stress Disorder (PTSD). Other anxiety disorders also included in DSM-IV are Panic Attack, Acute Stress Disorder, Anxiety Disorder Due to a General Medical Condition, Substance-Induced Anxiety Disorder and Anxiety Disorder Not Otherwise Specified.

Panic Attacks can occur in the context of any anxiety disorder as well as other mental disorders e.g. MDD and it is not a codable disorder. Symptoms of Acute Stress Disorder are experienced during or immediately after the trauma, last for at least 2 days, and either resolve within 4 weeks after the conclusion of the traumatic event or the diagnosis is changed to Post-traumatic Stress Disorder. Anxiety Disorder Not Otherwise Specified includes disorders with prominent anxiety or phobic avoidance that do not meet criteria for any specific Anxiety Disorder or Adjustment Disorder (American Psychiatric Association 2000b).

4.3.3.1 Epidemiology of anxiety disorders

The prevalence rates of anxiety disorders have been found to vary considerably between studies. In a review of 41 separate studies, several factors were found to be associated with heterogeneity among prevalence rates, including diagnostic criteria and diagnostic instrument used, sample size of the study, country studied and response rate (Somers et al. 2006). The prevalences, age of onset and female-male − ratio of Panic Disorder, Agoraphobia, Social Phobia, Specific Phobia, Generalized Anxiety Disorder, Obsessive Compulsive Disorder and Post-traumatic Stress Disorder and any anxiety disorder are presented in Table 2.

4.3.3.2 Etiology of anxiety disorders

The etiology of anxiety disorders includes a multiplicity of factors, such as genetic and other biological, psychological and social determinants, which are mediated by a range of risk and protective factors (Hettema et al. 2001; Fricchione 2004; Jenike 2004; Katon 2006; Schneier 2006).

Hypothesis of a common underlying factor for both anxiety and depressive disorders has also been proposed (Krueger 1999a). In a 15-year longitudinal study of depression and anxiety (GAD and panic disorder) among 591 young adults, the major finding was the longitudinal stability of comorbid anxiety and depression disorders, suggesting a common underlying diathesis for at least part of these disorders (Merikangas et al. 2003). Also genetic studies have revealed the relatedness of anxiety and depressive disorders. When studying more than 5600 members of twin pairs, Kendler et al. (2003a) found that when dividing common psychiatric and substance use syndromes into two broad groups of internalizing and externalizing disorders, anxiety disorders (GAD, panic disorder and

specific phobias) and major depressive disorder belonged both to internalizing disorders. Within the internalizing disorders, two genetic factors, anxious-misery (MDD, GAD and panic disorder partly) and fear (animal and situational phobia and panic disorder partly) could be detected to predispose to disorders, and genetic factors were found to be largely responsible for the pattern of this comorbidity (Kendler et al. 2003a). Later exposure to unique environmental experiences may explain why one disorder vs. another develops in genetically vulnerable individuals (Kendler et al. 2003a).

4.3.3.3 Clinical characteristics of anxiety disorders

The central clinical characteristics of Panic Disorder, Agoraphobia, Social Phobia, Specific Phobia, Generalized Anxiety Disorder, Obsessive Compulsive Disorder and Post-traumatic Stress Disorder are presented in Table 3.

Table 2. The prevalences, age of onset and female-male – ratio of essential anxiety disorders.

Anxiety Disorder	**Prevalence rate (%)**				**Age of onset**	**Female : Male**[5]
	World: Pooled prevalences of 41 studies. Somers et al. 2006		**Europe:** Wittchen and Jacobi 2005	**Finland:** Pirkola et al. 2005		
	12-month (95% CI)	Lifetime (95% CI)	12-month median	12-month		
Panic Disorder	0.99 (0.55-1.5)	1.2 (0.7-1.9)	1.8	1.9	early to middle 20s[1]	2-3.5:1
Agoraphobia	1.6 (1.0-2.3)	3.8 (2.5-5.6)	1.3	1.2		2-4:1
Social Phobia	4.5 (3.0-6.4)	3.6 (2.0-5.6)	2.3	1.0	12-17 years[2]	1.2-2.6:1
Specific Phobia	3.0 (0.98-5.8)	5.3 (3.4-7.9)	6.6		childhood or early adolescence[6]	2-4:1
GAD	2.6 (1.4-4.2)	6.2 (4.0-9.2)	1.7	1.3	< 25 years[3]	1.5-2:1
OCD	0.54 (0.28-0.86)	1.3 (0.86-1.8)	0.7		22 - 36[4]	1:1
PTSD	1.2 (0.09-3.4)	2.1 (0.4-4.9)			can occur at any age[7]	2:1[7]
Any anxiety disorder	10.6 (7.5-14.3)	16.6 (12.7-21.1)		4.2		2:1

[1] Katon 2006, [2] Schneier 2006, [3] Fricchione 2004, [4] Jenike 2004, [5] Somers et al. 2006, [6] Harvey and Rapee 2002, [7] Keane et al. 2006

4.3.3.4 Course and outcome of anxiety disorders

Some main features of clinical course and outcome of Panic Disorder, Agoraphobia, Social Phobia, Specific Phobia, Generalized Anxiety Disorder, Obsessive Compulsive Disorder and Post-traumatic Stress Disorder are presented in Table 4.

Table 3. The central clinical characteristics of Panic Disorder, Agoraphobia, Social Phobia, Specific Phobia, GAD, OCD and PTSD in DSM-IV.

Anxiety Disorder	Clinical picure of anxiety	Avoidance behaviour
Panic Disorder	Recurrent, also spontaneous panic attacks, with or without agoraphobia.	Without agoraphobia, no. With agoraphobia, yes.
Agoraphobia	Fear of developing "panic-like symptoms", without having Panic Disorder.	Avoidance of places or situations from which escape might be difficult.
Social Phobia	Anxiety in feared social situations.	Avoidance of social and performance situations.
Specific Phobia	Anxiety, if exposured to feared object or situation.	Avoidance of phobic situations.
GAD	Chronic anxiety and difficulty to control the worry.	No avoidance behaviour.
OCD	Obsessions and compulsions.	Avoidance of the content of obsessions.
PTSD	Re-experience of the traumatic event, symptoms of increased arousal, numbing of general responsiveness.	Avoidance of stimuli associated with the trauma.

Table 4. Some main features of course and outcome of Panic Disorder, Agoraphobia, Social Phobia, Specific Phobia, GAD, OCD and PTSD.

Anxiety Disorder	Clinical course	Outcome
Panic Disorder[1]	Usually relapsing-remitting disorder.	Approximately 20% of patients have a chronic course. Coexisting MDD, agoraphobia and personality disorder predicts more persistant symptoms of anxiety.
Agoraphobia[8]	Often continuous, lifelong.	May persist for years and be associated with considerable impairment.
Social Phobia[2]	Often continuous, lifelong.	May attenuate in severity or remit during adulthood and fluctuate with life stressors and demands.
Specific Phobia[9]	Often continuous, lifelong.	Phobias that persist into adulthood remit only infrequently (around 20% of cases).
GAD[3]	Chronic, but fluctuates, often worsens during times of stress.	Chronic, about 40% in remission at five years. Low remission rate associates with personality disorder and poor-quality family relationships.
OCD[4,7]	Often long delay in diagnosis. The symptoms wax and wane over time.	May remit, but can be relapsing or chronic. Up to 40% of patients who present to psychiatrists fail to respond to treatment.
PTSD[5,6]	Often Acute Stress Disorder precedes. Symptoms usually begin within 3 months after the trauma and may reactivate in response to reminders of the original trauma, life stressors or new traumatic event.	50% in remission at 2 years, 30% having the disorder at 6 years.

[1] Katon 2006, [2] Schneier 2006, [3] Fricchione 2004, [4] Heyman et al. 2006, [5] Bisson 2007, [6] Keane et al. 2006, [7] Jenike 2004, [8] Pollack et al. 2002, [9] Craske et al. 1996

4.4 Dimensions of temperament and personality

4.4.1 Definition of the concepts

The term temperament refers to individual differences in general mood or qualities of emotional responses that appear early in life, remain fairly stable, are inherited and are based in biological processes (Bates 2000; Pervin et al. 2005). The pattern of self-regulation is also an essential part of temperament (Rothbart 1989; Bates 2000). Thus, temperament can be seen as the early appearing biological core of later adult personality. There exist several theories of temperament with different emphasis and number of temperament dimensions. Adult temperament theories include the theories of Strelau (1993) and Cloninger (1993) and child temperament theories include the theories of Thomas and Chess (1977), Buss and Plomin (1975), Kagan (1986) and Rothbart and Derryberry (1981).

In contrast to temperament, many aspects of personality do not have their basis in inherited biology. Personality can be conceptualized as a large entity of individual differences including values, motives, attitudes, needs, coping mechanisms, capabilities, attainments and self-esteem. Thus, personality develops from the temperament through experiences, maturation and interaction with environment. (Pervin et al. 2005)

In the trait theories of personality it is assumed that individuals possess broad predispositions, called traits, to respond in particular ways, i.e. personality traits refer to consistent pattern in the way an individual behaves, feels and thinks. The traits provide a way to summarize how one person differs from another and to make predictions about the person's future behaviour (Pervin et al. 2005). According to the trait theories, at its simplest level, behaviour can be considered in terms of specific responses that can futher be linked together as habits, and habits grouped as traits. Finally various traits may be linked together to form higher-order factors or dimensions. To identify traits and higher-order factors, a statistical technique of factor analysis is used, where the correlations among a set of trait terms in language are analysed in order to determine those variables that increase or decrease together (Pervin et al. 2005). Several trait theories of personality have been developed including the 16-factor model (Cattell 1965), the three factor model (Eysenck and Eysenck 1975) and the five factor model (Costa Jr. and McCrae 1992).

In adulthood, there is convergence between temperament and personality trait constructs. Substantial measurement overlap between temperament and personality measures has often been found (Zuckerman and Cloninger 1996; De Fruyt et al. 2000) and the term temperament has sometimes been used synonymously with personality or personality dimension (Eysenck 1991), and it has been suggested that temperament characteristics may be understood as

early-appearing personality traits (Buss and Plomin 1984). However, until more longitudinal studies from infancy to adulthood has been taken place, the question how temperament and personality dimensions relate to each other remains open.

Recently, a comprehensive framework of personality psychology has been proposed for understanding the whole person (McAdams and Pals 2006). According to this proposal, personality consists of five big principles that suggest a framework for integrating personality traits with those self-defining features of psychological individuality, constructed in response to situated social tasks and the human need to make meaning in culture. In this model, personality is conceived as an individual's unique variation on the general evolutionary design for human nature, expressed as a developing pattern of dispositional traits, characteristic adaptations and self-defining life narratives, complexly and differentially situated in culture and social context

4.4.2 Personality dimensions and their measurement

Although there has been a long debate on the sufficient number of personality traits during the last decades, no consensus exists. However, almost all major theories of personality include two broad personality dimensions, neuroticism and extraversion, describing negative and positive trait entities, respectively (Watson et al. 1999). Nowadays more and more support among trait theorists is emerging around the five-factor model, consisting of Neuroticism, Extraversion and three additional factors (Agreeableness, Conscientiousness and Openness to new experience), each factor having six facets. Support for this model comes from factor analyses of large sets of trait terms in the language, cross-cultural research testing the universality of trait dimensions and the relation of trait questionnaires to other questionnaires and ratings (Pervin et al. 2005). Several five-factor solutions and questionnaires exists, perhaps the most widely used is NEO-PI-R (Table 5.) (Costa Jr. and McCrae 1992).

Several scales have been developed to measure personality dimensions. The questionnaires are usually used as self-rated, but can also be used as observer- or peer-rated (Pervin et al. 2005). These questionnaires include the 57-item Eysenck Personality Inventory (EPI, Eysenck and Eysenck 1964), the Cattell's 16 Personality Factors Questionnaire (16 PF, Cattell 1965), the 567-item Minnesota Multiphasic Personality Inventory (MMPI, Dahlstrom et al. 1975), the 135-item Karolinska Scales of Personality (KSP, Schalling 1986), the 276-item Multidimensional Personality Questionnaire (MPQ, Tellegen et al. 1988) the 51-item Munich Personality Test (MPT, von Zerssen et al. 1988), the 10-item Positive and Negative Affect Schedule (PANAS, Watson et al. 1988), the 89-item Zuckerman and Kuhlman's Personality Questionnaire (ZKPQ, Zuckerman et al. 1993) and the 240-item Five-Factor Personality Inventory-Revised (NEO-PI-R, Costa Jr. and McCrae 1992). While the overall composition of these personality trait inventories vary markedly, all include and measure the essentially similar dimensions of neuroticism and extraversion (Clark et al. 1994; Enns and Cox 1997).

Eysenck Personality Inventory (form A and B) (Eysenck and Eysenck 1964), its forerunner the Maudsley Personality Inventory (Eysenck 1959) and its successor Eysenck Personality Questionnaire (Eysenck and Eysenck 1975) and its revised version EPQ-R (Eysenck and Eysenck 1991) have been developed by factor analysis and all measure two major dimensions of personality, extraversion-introversion and neuroticism (alternatively called emotional stability versus instability). A third dimension, called Psychoticism (P), was added into EPQ and EPQ-R. Individuals high on P dimension tend to be solitary, intensive, uncaring about others and opposed to accepted social custom (Eysenck and Eysenck 1975). In addition, a fourth factor, called Lie scale, was included in EPI, EPQ and EPQ-R to detect individuals "faking good" (Eysenck and Eysenck 1964). Corresponding scales on EPI form A and B, as well as on EPI and on EPQ correlate highly and are assumed to measure identical dimensions of personality (Eysenck and Eysenck 1964; Eysenck and Eysenck 1975). Several validation studies of N and E dimensions have been done around the world (Barrett et al. 1998), and also in Finland using EPQ (Eysenck and Haapasalo 1989).

4.4.2.1 Neuroticism

Neuroticism (N) is characterized by proneness to anxiety, emotional instability and self-consciousness. A high neuroticism scorer is someone who tends towards anxiety and depression, worries, has bad sleep and psychosomatic disorders, allows emotions to affect judgement and is preoccupied with things that might go wrong, whereas low N scorer recovers quickly after an emotionally upsetting experience and is generally calm and unworried (Eysenck and Eysenck 1964). The core of neuroticism and other similar dimensions, including negative emotionality (NE, Tellegen et al. 1988) and negative affectivity (NA, Watson et al. 1988) is believed to be sensitivity to negative stimuli (Clark et al. 1994). N/NE/NA have also been linked with an aversive motivational system (the behavioural inhibition system), which is believed to increase non-specific arousal and attention to threat-related stimuli and inhibit behaviour (Clark et al. 1994). Moreover, it has been hypothesized that neuroticism is a reflection of individual differences in the activation thresholds of the sympathetic nervous system (fight/flight response) (Eysenck 1990).

Table 5. The Big Five trait factors, facets and factor definitions.

Factor	Factor definition	Facets
Neuroticism (N)	Assesses adjustment vs. emotional instability. Identifies individuals e.g. prone to psychological distress.	Anxiety, Self-consciousness, Depression, Vulnerability, Impulsiveness, Angry Hostility.
Extraversion (E)	Assesses quantity and intensity of interpersonal interaction; activity level; need for stimulation and capacity of joy.	Gregariousness, Activity Level, Assertiveness, Excitement Seeking, Positive Emotions, Warmth.
Openness (O)	Assesses proactive seeking and appreciation of experience for its own sake; toleration for and exploration of the unfamiliar.	Fantasy, Aesthetics, Feelings, Ideas, Actions, Values.
Agreeableness (A)	Assesses the quality of one's interpersonal orientation along a continuum from compassion to antagonism in thoughts, feelings, and actions.	Straightforwardness, Trust, Altruism, Modesty, Tendermindedness, Compliance.
Conscientiousness (C)	Assesses the individual's degree of organization, persistence, and motivation in goal-directed behaviour.	Self-discipline, Dutifulness, Competence, Order, Deliberation, Achievement Striving.

The distribution of neuroticism scores in the population approximates to a normal curve, women scoring usually higher on N than men (Eysenck and Eysenck 1964). Neuroticism and extraversion dimensions have been found to have a negative correlation with each other (Eysenck and Eysenck 1964), especially amongst high N scorers (Buckingham et al. 2001). A negative correlation between N and age has also been reported (Eysenck and Eysenck 1964; Eysenck and Eysenck 1975). Both test-retest correlation (r=0.8-0.9) and internal consistency (alpha from 0.84 to 0.85) have been found to be good (Eysenck and Eysenck 1964; Eysenck and Eysenck 1975). EPI or EPQ N score correlates with N or similar scores from other inventories, including NEO-PI-R-N (r=0.77) and ZKPQ-N-Anxiety (r=0.80) (Aluja et al. 2002) as well as PANAS-Negative Affect Scale (r=0.58)(Watson et al. 1999). In the Finnish validation study of EPQ, internal consistency of N was found to be good (Cronbach's alpha 0.84), females scored higher on N than males (mean 12.25, sd 4.87 vs. 10.13, sd 5.02) and N correlated negatively with E (r=-0.20 for females; r=-0.22 for males)(Eysenck and Haapasalo 1989).

4.4.2.2 Extraversion

Extraversion involves positive emotionality, energy and dominance. A typical extravert is sociable, likes parties, has many friends, needs to have people to talk to and does not like reading or studying by him/herself, whereas a typical introvert is a quiet, retiring sort of person, introspective, fond of books rather than people, is reserved and distant except to intimate friends (Eysenck and Eysenck 1964). The core of extraversion and other similar dimensions including positive emotionality (PE, Tellegen et al. 1988) and positive affectivity (PA, Watson et al. 1988) is believed to be affective, reflecting a tendency to experience positive mood states. E/PE/PA has also been linked to behavioural activation system and to the behavioural facilitation system (Clark et al. 1994). Poor regulation of the behavioural facilitation system has been found to associate, on the low end of E/PE/PA dimension, with low energy and activity levels, withdrawal, decreased cognitive capacity, anhedonia and depressed mood (Clark et al. 1994). Moreover, it has been hypothesized that extraversion reflects cortical arousal, introverts being chronically overaroused (anxious) and extraverts underaroused (bored) (Eysenck 1990).

The distribution of extraversion scores in the population approximates to a normal curve, men scoring usually higher on E than women (Eysenck and Eysenck 1964). A negative correlation between E and age has been found (Eysenck and Eysenck 1964; Eysenck and Eysenck 1975), slightly stronger among males than females (Eysenck and Eysenck 1975). Both test-retest correlation (r=0.80-0.97) and internal consistency (alpha from 0.84 to 0.86) have been found to be good (Eysenck and Eysenck 1964; Eysenck and Eysenck 1975). EPI or EPQ E score correlates with E or similar scores from other inventories, including NEO-PI-R-E (r=0.77) and ZKPQ-Surgency (r=0.74) (Aluja et al. 2002), as well as PANAS-Positive Affect Scale (r=0.51) (Watson et al. 1999).

In the Finnish validation study of EPQ, internal consistency of E was found to be good (Cronbach's alpha 0.86), males scored slightly higher than females (mean 10.58, sd 4.80 vs. 10.01, sd 4.86) (Eysenck and Haapasalo 1989).

4.4.3 Temperament dimensions and their measurement

Several scales have been developed to measure temperament dimensions. The questionnaires are usually used as self-rated, but can also be used as observer- or peer-rated (Pervin et al. 2005). Inventories measuring temperament in adults include the 27-item Emotionality, Activity and Sociability-Inventory (EAS, Buss and Plomin 1975), the 54-item Revised Dimensions of Temperament Survey (DOTS-R, Windle and Lerner 1986), the 240-item Temperament and Character Inventory-Revised (TCI-R, Cloninger 1994), the 20-item Formal Characteristics of Behaviour-Temperament Inventory (FCB-TI, Strelau and Zawadzki 1993) and the 110-item Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Interview (TEMPS, Akiskal and Mallya 1987; Akiskal et al. 1998).

4.4.3.1 Cloninger's temperament and character dimensions

A unified biosocial theory of personality consisting of neurobiologically based dimensions of temperament and characterological aspects of personality was proposed by Cloninger. This theory is based on information from several sources: family studies, longitudinal development research, psychometric descriptions of personality structure, neuropharmacological and neuroanatomical studies of conditioning and learning in man and animals (Cloninger 1986, 1987). The Tridimensional Personality Questionnaire (Cloninger 1987) was design to test the three temperament dimension of Novelty Seeking (NS), Harm Avoidance (HA) and Reward Dependence (RD). After a new temperament dimension of Persistence (P), originally scored as a component of RD, and three character dimensions of Self-Directedness, Cooperativeness and Self-Transcendence were added to the scale, the name was changed as the Temperament and Character Inventory (Cloninger et al. 1993). Later a revised version, TCI-R, has also been published, with a five-point Likert scale, which allows better estimates of the subscales, 51 items rewritten, and 3 subscales added to P and 1 to RD (Pelissolo et al. 2005).

The psychometric properties of the various forms of the instrument have been evaluated in several countries, including TPQ in USA (Cloninger et al. 1991), England (Otter et al. 1995), Yugoslavia (Svrakic et al. 1991) and Finland (Miettunen et al. 2004); TCI in USA (Cloninger et al. 1993), Sweden (Brandstrom et al. 1998), the Netherlands (Duijsens et al. 2000), France (Pelissolo and Lepine 2000) and Finland (Miettunen et al. 2004) and TCI-R in Italy (Fossati et al. 2007), Spain (Gutierrez-Zotes et al. 2004), France (Pelissolo et al. 2005), Belgium (Hansenne et al. 2005) and in Finland among adolescents (Lindgren 2002). TCI and TCI-R scales can be used interchangeably (Pelissolo et al. 2005; Fossati et al. 2007).

4.4.3.1.1 Temperament dimensions

The different temperament dimensions are defined in terms of basic stimulus-response characteristics. *Novelty Seeking* is thought to be related to the behavioural activation system (Cloninger 1987), to predict facility in incentive activation (Cloninger 1987), is linked to the brain's dopamine-system (Cloninger 1987) and the suggested associated basic emotional state is anger (Svrakic et al. 1996; Puttonen et al. 2005). Individuals high in NS tend to be quick-tempered, excitable, exploratory, curious, enthusiastic, exuberant, easily bored, impulsive and disorderly. NS has four subscales called Exploratory Excitability, Impulsiveness, Extravagance and Disorderliness (Cloninger 1994).

Harm Avoidance is thought to be related to the behavioural inhibition system (Cloninger 1987), to predict facility in the formation of conditioned signals of punishment (Cloninger 1987), is linked to to brain's serotonin-system (Cloninger 1987) and the suggested associated basic emotional state is fear (Svrakic et al. 1996; Puttonen et al. 2005). Individuals high in HA tend to be cautious, careful, fearful, tense, apprehensive,

nervous, timid, doubtful, discouraged, insecure, passive, negativistic or pessimistic even in situations that do not worry other people. HA has also four subscales called Anticipatory Worry, Fear of Uncertainty, Shyness, and Fatiguability and Asthenia (Cloninger 1994).

Reward Dependence is thought to be related to the maintenance system (Cloninger 1987), to predict facility in the formation of conditioned signals of reward, particularity of verbal signals of social approval (Cloninger 1987), is linked to the release of noradrenalin in the autonomous nervous system (Cloninger 1987) and the suggested associated basic emotional state is disgust/love (Svrakic et al. 1996; Puttonen et al. 2005). Individuals high in RD tend to be tender-hearted, loving and warm, sensitive, dedicated, dependent and sociable. RD has four subscales called Sentimentality, Openness, Attachment and Dependence (Cloninger 1994).

Persistence is linked to perseverance in behaviour despite frustration and fatigue and involves individual differences in the ability to convert a signal of punishment into a signal of eventual reinforcement (Cloninger 1987). Individuals high on P tend to be industrious, hard-working, persistent and stable. P has four subscales called Eagerness, Work Hardened, Ambitious and Perfectionist (Cloninger 1994).

The distribution of temperament scores in the population approximates to a normal curve. In a meta-analysis of 32 studies estimating gender differences in temperament dimensions, it was found that women scored higher in RD and HA, no difference was found in NS and P (Miettunen et al. 2007). NS has been found to correlate negatively (Cloninger 1994; Brandstrom et al. 2001), whereas HA positively with age (Brandstrom et al. 2001). Both test-retest reliability (NS: r=0.91-0.93; HA: r=0.81-0.89; RD: r=0.83-0.86,; P: r=0.83-0.90) and internal consistency (NS: alpha=0.80; HA: alpha=0.92; RD: alpha=0.84 and P: alpha=0.92) have been found to be good using TCI-R (Pelissolo et al. 2005). A negative correlation has been found between NS and both HA (r=-0.38) and P (r=-0.22), whereas a positive correlation between NS and RD (r=0.21) (De Fruyt et al. 2000).

Temperament dimensions have been found to correlate with various other scales, including EPQ (HA and N: r=0.59; HA and E: r=-0.53; NS and E: r=0.44) and ZKPQ (HA and N-Anxiety: r=0.66; NS and Impulsive Sensation: r=0.68) (Zuckerman and Cloninger 1996), as well as NEO-PI-R (HA and N: r=0.54; HA and E: r=-0.57, NS and E: r=0.43; RD and E: r=0.45) (De Fruyt et al. 2000) .

In a Finnish study using TPQ and TCI, females scored higher than males in HA, NS and RD, whereas males scored higher than females in TCI-P (Miettunen et al. 2004).

4.4.3.1.2 Character dimensions

Three character dimensions were added to the TCI questionnaire to assess individual differences in self-concept about goals and values and to distinguish individuals with personality disorder. As a result of differences in character development, individuals with the same temperament may behave differently (Cloninger 1994).

Self-Directedness (SD) is supposed to be based on the concept of the self as an autonomous individual, and from the concept are derived feelings of personal integrity, honour, self-esteem, effectiveness, leadership and hope (Cloninger 1994).

Co-operativeness (C) is supposed to be based on the concept of the self as an integral part of humanity or society, and from this concept are derived feelings of community, compassion, conscience and charity (Cloninger 1994).

Self-Transcendence (ST) is supposed to be based on the concept of self as an integral part of the universe and its source, and from this concept of the self are derived feelings of mystical participation, religious faith and unconditional equanimity and patience (Cloninger 1994).

The distribution of character scores in the population approximates to a normal curve. No clear and consistent gender differences have been found in character scores.

Compared to males, females score usually higher (Cloninger 1994; Pelissolo et al. 2005) or not (Pelissolo and Lepine 2000) on C; lower (Pelissolo and Lepine 2000), higher (Pelissolo et al. 2005) or neither (Cloninger 1994) on SD and higher (Pelissolo and Lepine 2000) or not (Cloninger 1994) on ST. Age has been found to correlate positively (Cloninger 1994; Pelissolo et al. 2005) or not (Pelissolo and Lepine 2000) with SD; positively (Cloninger 1994; Pelissolo et al. 2005) or not (Pelissolo and Lepine 2000) with C and positively (Pelissolo et al. 2005) or not (Cloninger 1994; Pelissolo and Lepine 2000) with ST. Both test-retest reliability (SD: r=0.82-0.93; C: r=0.88-0.90; ST: r=0.82-0.87) and internal consistency (SD: alpha=0.88; C: alpha=0.81; ST: alpha=0.85) have been found to be good using TCI-R (Pelissolo et al. 2005).

Character dimensions have been found to correlate with other scales, including NEO-PI-R (SD and N: r=-0.63; SD and E: r=0.29; C and E: r=0.20; ST and E: r=0.25) (De Fruyt et al. 2000) and also with other TCI dimensions (SD and HA: r=-0.47, C and RD: r=0.54; C and SD: r=0.57) (Cloninger 1994).

4.4.4 Heritability of temperament and personality dimensions

Personality traits have been found to be substantially influenced by genes (Bouchard and Loehlin 2001). In a review of four twin studies, the broad heritabilities of self- or peer-reported measures for extraversion and neuroticism were found to be 0.49 and 0.41, respectively (Bouchard and Loehlin 2001). In addition there is evidence of gender-specific heritability for N (Fanous et al. 2002). The genetic factors have been shown to account also for the variability of Cloninger's temperament dimensions, as heritablities for HA, NS, RD and P have been found to be 0.41, 0.39, 0.35 and 0.30, respectively (Gillespie et al. 2003). The remaining percentage of the variability of the personality dimensions probably comprises causes such as gene-environment interactions, chance factors in development and errors of measurement (Bouchard and Loehlin 2001).

Temperament and character may not differ greatly in heritability. Contrary to theoretical expectations the familial aggregation for the character dimensions has also been substantial, as the heritabilities for SD, C and ST have been found to be 0.35, 0.27 and 0.44, respectively (Gillespie et al. 2003).

Molecular genetic studies of personality have mostly concerned the possible links between Novelty Seeking/Extraversion and type 4 dopamine receptor (DRD4) gene and Neuroticism/ Harm Avoidance and serotonin transporter (5HTTLPR) gene (Ebstein 2006). The results of the association between NS and DRD4 polymorphism have been inconsistent (Schinka et al. 2002; Ebstein 2006) indicating that there might be unknown moderators like the childhood environment (Keltikangas-Järvinen et al. 2004). The effect size of the association between 5HTTLPR gene and anxiety-related personality traits has been found to be small, but significant in most (Ebstein 2006), but not all (Willis-Owen et al. 2005) studies. Moreover, it has been found that the individual variation in the level of neuroticism is partly moderated by genetic factors e.g. the amygdala response to emotional face processing has been found to be moderated by functional variation in the serotonin transporter gene (Hariri et al. 2002).

4.4.5 Stability of temperament and personality dimensions

The stability of personality in the population level has been evaluated by using mean-level and rank-order consistency (Matthews et al. 2003). Mean-level consistency reflects whether groups of people increase or decrease on trait over time, whereas rank-order consistency refers to the relative placement of individuals within a group (Matthews et al. 2003).

In a meta-analysis (Roberts and DelVecchio 2000) of 152 longitudinal studies from childhood to old age investigating the rank-order consistency of personality traits, it was concluded that traits are quite consistent over the life course although trait consistency increased from 0.31 in childhood, to 0.54 during the college years, to 0.64 at age 30 and then reached a plateau around 0.74 between ages 50 to 70.

In another meta-analysis (Roberts et al. 2006a) of 92 studies determining mean-level change in personality traits among individuals from 10 years to 101years, the results showed that of the six trait categories (Extraversion, divided into social vitality and social dominance; Agreeableness; Conscientiousness; Emotional stability and Openness) four demonstrated significant change in middle and old age. Social dominance, conscientiousness and emotional stability increased, especially from age 20 to 40, whereas social vitality and openness increased in adolescence but decreased in old age. Agreeableness increased only in old age. In an internet study of 132,515 adults from 21-60 years studying mean-level change of personality, it was also found that C and A increased throughout early and middle adulthood and neuroticism declined among women but did not change among men (Srivastava et al. 2003). Thus, although population studies demonstrate high rank-order consistency of personality traits after the age of 30 years, they simultaneously also demonstrate significant mean-level change until old age, suggesting that change in basic personality configurations is more quantitative than qualitative.

Recently the attention of personality development research has turned to the causes of personality change. It has been hypothesized that personality changes are not only the result of endogenous biological mechanisms unaffected by environmental influences (McCrae et al. 2000), but also of dynamic transactions between individual characteristics and the environment (Roberts et al. 2005). The social investment theory suggests that personality maturation during adulthood takes place as individuals assume and commit to adult social roles (Roberts et al. 2005) and personality change can take place even in middle adulthood (van Aken et al. 2006). According to this model, taking adult responsibilities in the domains of work, family, religion and volunteerism is associated with increase in conscientiousness, agreeableness and emotional stability (Roberts et al. 2005), although there are also individuals who show personality trait change opposite of the normative pattern, confirming that individual differences in change are the rule, not the exception (Roberts et al. 2006b). Another new theory concerning the causes of personality change is narrative appoach i.e. how individuals create meaning and purpose in their lives through the construction of life stories (McAdams 2001). Changes and new developments in how individuals interpret their lives may trigger corresponding changes in patterns of thinking, feeling, and behaving - i.e. personality traits - over time (Pals 2006).

4.4.6 Personality disorders and temperament and personality dimensions

DSM-IV has 10 personality disorders and additionally Personality Disorder Not Otherwise Specified. In DSM-IV personality disorder has been specified as an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment. Personality disorders can be grouped into three clusters based on descriptive similarities. Cluster A includes the Paranoid, Schizoid and Schizotypal Personality Disorders. Individuals with these disorders often appear odd or eccentric. Cluster B includes the Antisocial, Borderline, Histrionic and Narcissistic Personality Disorders. Individuals with these disorders often appear dramatic, emotional or erratic. Cluster C includes the Avoidant, Dependent and Obsessive-Compulsive Personality Disorders. Individuals with these disorders appear anxious or fearful (American Psychiatric Association 2000b).

The diagnostic system used in DSM-IV and ICD-10 represents the categorical perspective of personality disorders, suggesting that these disorders are qualitatively distinct clinical syndromes. The term "dimensional approach" has been used at least in two distinct ways i.e. either each separate personality disorder (PD) is conceptualized as a continuum, or that the fundamental dimensions underlying the disorders are not the PD's themselves but the personality traits that compose the disorders. This latter type of dimensional perspective assumes that personality disorders represent maladaptive variants of personality traits that emerge imperceptibly into normality and into one another (Skodol et al. 2005; Clark 2007). Moreover, personality clusters may be viewed as dimensions representing spectra of personality dysfunction on a continuum with axis I disorders (Clark 2007). Recently, a prototype matching approach to personality disorder diagnosis has been developed, in which each PD is presented by experts in its ideal or "pure" form, whereby the diagnosticians rate the overall similarity between the patient and the prototype by using e.g. the facets of the Five-Factor Model (Lynam and Widiger 2001) or a 5-point rating scale and considering the prototype as a whole rather than counting individual symptoms (Westen et al. 2006).

Of personality dimensions, neuroticism has been found to associate positively with all personality disorders (Deary and Peter 1998; Brieger et al. 2000; Duggan et al. 2003; Saulsman and Page 2004; Moran et al. 2006). Low extraversion, on the other hand, has also been found to have an association with all personality disorders (Duggan et al. 2003), or with only some of cluster A or C (Deary and Peter 1998; Brieger et al. 2000; Saulsman and Page 2004; Furnham and Crump 2005) or borderline personality disorders (Saulsman and Page 2004). In contrast, extraversion has been found to have a positive association with histrionic and/or narcissistic personality disorders (Deary and Peter 1998; Brieger et al. 2000; Saulsman and Page 2004; Furnham and Crump 2005).

Of TCI dimensions, low SD and C has been found to associate with the number of personality disorder symptoms and the presence of any personality disorder (Svrakic et al. 1993), or C, all but histrionic personality disorder symptoms (Svrakic et al. 2002). High ST has been found to associate with the symptoms of histrionic, narcissistic, borderline, schizotypal and paranoid personality disorders (Svrakic et al. 2002), whereas low ST with symptoms of schizoid personality disorder (Svrakic et al. 1993). Thus, ST might be able to distinguish between schizoid and schizotypal personality disorders (de la Rie et al. 1998). Patients with cluster A personality disorder have been found to have low RD and high HA (Svrakic et al. 1993, 2002; Farabaugh et al. 2005), with cluster B disorder high NS (Svrakic et al. 1993; Farabaugh et al. 2005) or high NS and HA (Svrakic et al. 2002) and with cluster C disorder high HA (Svrakic et al. 1993; Farabaugh et al. 2005) or both high HA and NS (Svrakic et al. 2002).

Overall, personality dimensions seem to associate with personality disorders. However, e.g. the TPQ scores in relation to PD's have been found to explain only a part of the variance, suggesting that personality traits are one contributing factor among others to PD's (Farabaugh et al. 2005).

4.5 Temperament and personality dimensions and affective disorders

The relationship between personality and affective disorders is complex. Personality features may have a common cause with affective disorders, may predispose an individual to affective disorders, be shaped by repeated episodes of the illness, modify the clinical picture of the illness, be an attenuated expression of the disorder or be state-dependent concomitants of affective disorders (Shea and Yen 2005; Brandes and Bienvenu 2006).

The association between affective disorders and personality has been studied extensively. In these studies personality functioning has been conceptualized in numerous ways, including research on sociotropy/autonomy and dependency/self-criticism derived from cognitive and psychoanalytic theories of affective disorders, respectively; on personality disorders; on personality traits derived from factor-analytic approaches; and on Cloninger's temperament and character dimensions (Shea and Yen 2005; Brandes and Bienvenu 2006).

4.5.1 Temperament and personality dimensions and depression

4.5.1.1 Neuroticism

A positive correlation between the dimension of neuroticism and depressive symptoms (Fergusson et al. 1989; Saklofske et al. 1995) as well as depressive disorders (Katz and McGuffin 1987; Farmer et al. 2002; Bienvenu et al. 2004; Cuijpers et al. 2005) has been demonstrated in numerous cross-sectional studies over the decades. Neuroticism has been found to be markedly affected by current mood state (Coppen and Metcalfe 1965; Kendell and DiScipio 1968; Hirschfeld et al. 1983b; Kendler et al. 1993b; Shea et al. 1996; Ormel et al. 2004; Fanous et al. 2007) and to increase after an episode of depression in some (Hirschfeld et al. 1989; Kendler et al. 1993b; Fanous et al. 2007) but not all (Duggan et al. 1991; Shea et al. 1996; Ormel et al. 2004) reports. In addition high N has been found to predict poorer course and outcome of depression over follow-up periods ranging from 6 months to 18 years (Hirschfeld et al. 1986; Duggan et al. 1990; Kendler et al. 1997; Mulder 2002; Melartin et al. 2004), even after controlling for the severity of baseline depression (Duggan et al. 1990).

The view that high neuroticism is a risk factor for depression is supported by several prospective studies, in which neuroticism has been measured in the premorbid phase. In such studies, not only future depressive episodes have been found to be predicted by neuroticism (Hirschfeld et al. 1989; Boyce et al. 1991; Kendler et al. 1993b, 2006a; Fanous et al. 2007) or neuroticism-like traits (Nyström and Lindegård 1975; Angst and Clayton 1986; Rorsman et al. 1993) but also first onset depressive episodes by neuroticism (Hirschfeld et al. 1989; Boyce et al. 1991; Kendler et al. 1993b, 2006a) or neuroticism-like trait (Rorsman et al. 1993). Recent epidemiological twin studies have suggested that a set of genetic risk factors influence both neuroticism and liability to depression (Kendler et al. 2006a; Kendler and Prescott 2006). Thus neuroticism seems not to be a risk mediator for depression, but rather an indicator i.e. the genetic risk for depression does not "run through" neuroticism itself. In addition, the genetic correlation between N and MDD in males and in females has been found to be +0.47 and +0.46, respectively, suggesting that substantial proportions of the genetic vulnerability to depression does not reflect in neuroticism (Kendler et al. 2006a). Overall, the evidence for supporting the vulnerability, spectrum or common-cause, state and pathoplasty models for N and depression are the most consistent, whereas the evidence for the complication or scar model is less consistent.

4.5.1.2 Extraversion

Extraversion has been reported to have a negative correlation with depressive symptoms (Saklofske et al. 1995) as well as depressive disorders (Farmer et al. 2002; Cox et al. 2004) in cross-sectional studies. Although low extraversion has been suggested to be a vulnerability factor for depression (Hirschfeld et al. 1983a; Kendler et al. 2006a) and high extraversion to even exert some protective effects against depression (Farmer et al. 2002), the premorbidly started prospective epidemiological studies among male conscripts (Angst and Clayton 1986) and among twins (Kendler et al. 1993b; Fanous et al. 2007), as well as two prospective clinical studies (Hirschfeld et al. 1989; Boyce et al. 1991) have not proved this to be a risk factor. Confusingly, in longitudinal studies, extraversion has been found to be affected by mood states (Kendell and DiScipio 1968; Hirschfeld et al. 1983a; Farmer et al. 2002) or not (Shea et al. 1996; Fanous et al. 2007). There are only a few (Kerr et al. 1974; Van Londen et al. 1998) studies examining the prognostic impact of E on depression, and the results have been inconsistent; in some studies low E has been associated with poorer outcome (Kerr et al. 1974), whereas in some not (Van Londen et al. 1998). Overall, the role of extraversion as a risk factor for depression is more obscure than that of neuroticism.

4.5.1.3 Temperament and character dimensions

Harm Avoidance has been consistently shown to associate positively with depressive mood in non-clinical (Peirson and Heuchert 2001) and in clinical (Hansenne et al. 1999) cross-sectional studies and to predict future depressive symptoms in longitudinal non-clinical (Elovainio et al. 2004; Cloninger et al. 2006) studies, especially subscales HA3 (Shyness) and HA4 (Fatiguability and Asthenia) (Elovainio et al. 2004), but also to be altered by a depressed state (Joffe et al. 1993). Moreover, high HA has been able to predict familial vulnerability to major depression in a sib-pair study (Farmer et al. 2003). While NS does associate with some psychopathologic variables correlated with depression (Grucza et al. 2003), particularly the subscale NS 1 (Exploratory Excitability) (Hansenne et al. 1998), overall NS still appears to correlate negatively with depression per se (Farmer et al. 2003). High RD has been found to protect against the development of depression (Farmer et al. 2003) or to associate positively with depression (Ampollini et al. 1999), particularly with restless sleep and subjective symptoms of depression, when combined with high P (Grucza et al. 2003). The subscales NS2 (Impulsiveness) and RD1 (Sentimentality) as well as P has also been reported to increase the risk of depressive symptoms independently (Elovainio et al. 2004).

Of the character dimensions, low SD has been consistently found to associate with depression (Bayon et al. 1996; Farmer et al. 2003). Moreover, both low SD and HA have been reported to associate with a poor response to antidepressant medication in most (Joffe et al. 1993; Sato et al. 1999), but HA not in all (Newman et al. 2000) studies.

4.5.2 Temperament and personality dimensions and anxiety

4.5.2.1 Neuroticism and extraversion

Compared to depression, there are fewer studies on the relationship between anxiety and personality dimensions of neuroticism and extraversion. Fairly consistently high N has been recognized to associate with anxiety in prospective epidemiological twin (Hettema et al. 2004; Kendler et al. 2007), other non-clinical (Loo 1979; Moffitt et al. 2007) and clinical studies (Reich et al. 1986). Likewise, low E has been found to associate with anxiety in non-clinical (Loo 1979; Stewart et al. 2004) and clinical studies (Reich et al. 1986). Moreover, both N and E have been shown to be affected by anxiety state at least in panic and agoraphobic patients (Reich et al. 1986). Of specific anxiety disorders, individuals with social phobia or agoraphobia have tended to be both high in N and low in E (Bienvenu et al. 2004, 2007); with panic disorder, OCD or GAD high in N and overall average in E (Bienvenu et al. 2004), moreover low E has been reported not to be a vulnerability factor for GAD (Moffitt et al. 2007). Individuals with specific phobia have tended to be only slightly higher in N and lower in E than subjects without anxiety or depressive disorder (Bienvenu et al. 2004).

Although high neuroticism-like traits in late adolescence have been shown to predict the onset of anxiety disorders by young adulthood (Krueger 1999a) and in peacekeepers, the onset of post-traumatic stress disorder (Bramsen et al. 2000), as well as high N and low E in survivors of severe burns to predict the onset of PTSD during the following year (Fauerbach et al. 2000), the question whether these personality traits act as risk factors for anxiety remains open. Personality traits in these cases could have been either earlier manifestations of genetic and/or environmental influences that also affect the risk for anxiety disoders (Hettema et al. 2004) or prodromal symptoms of anxiety disorders (Brandes and Bienvenu 2006). Overall, high N and low E are found to be at least risk indicators for certain anxiety disorders, and both N and E be affected by anxiety state.

4.5.2.2 Temperament and character dimensions

Most consistently high HA and low SD have been associated with anxiety in clinical (Lyoo et al. 2001; Marteinsdottir et al. 2003) and non-clinical samples (Jiang et al. 2003; Matsudaira and Kitamura 2006). In addition, a negative correlation has been found between anxiety symptoms and either C in students (Jiang et al. 2003) or P, ST and C in patients with social phobia (Marteinsdottir et al. 2003), or NS in OCD patients (Lyoo et al. 2001), whereas a positive correlation has been reported between anxiety and RD in panic disorder patients (Ampollini et al. 1999). Moreover, HA, NS, SD and C have been found to be state-dependent on anxiety symptoms (Allgulander et al. 1998).

4.5.3 Temperament and personality dimensions and comorbid disorders of MDD

4.5.3.1 Neuroticism and extraversion

In epidemiological (Bienvenu et al. 2001; Weinstock and Whisman 2006), twin (Jardine et al. 1984; Andrews et al. 1990; Khan et al. 2005; Hettema et al. 2006; Kendler et al. 2007) and clinical (Bronisch and Hecht 1990; Cuijpers et al. 2005) studies, neuroticism appears to associate positively with the comorbidity of depressive and anxiety disorders, and has been found to be a risk factor for this comorbidity (Kendler et al. 2007) and explain even to one fourth of it (Khan et al. 2005). Also the comorbidity of depression and alcohol dependence (Khan et al. 2005) has been found to associate with high neuroticism, as well as depression and antisocial personality disorder (Khan et al. 2005) or any personality disorder (Davidson et al. 1985; Brieger et al. 2000).

Likewise, low extraversion has been found to associate with the comorbidity of depressive and anxiety disorders (Bienvenu et al. 2001; Cuijpers et al. 2005), but to explain only a very small proportion of it (Khan et al. 2005). A negative association has also been found between extraversion and the comorbidity of depression and alcohol dependence (Khan et al. 2005), and of depression and antisocial personality disorder (Khan et al. 2005) or any personality disorder (Brieger et al. 2003). Moreover, the number of comorbid anxiety disorders among MDD patients has been found to associate with high neuroticism and low extraversion (Cuijpers et al. 2005).

4.5.3.2 Temperament and character dimensions

There are only a few studies on the relationship of TCI dimensions with axis I and II comorbidity among MDD patients. In these studies, MDD with comorbid GAD has been found to be associated with high HA, whereas social anxiety disorder to high HA, low NS and RD (Ongur et al. 2005). MDD with the presence of comorbid OCD or panic disorder has been related to low NS , while simple phobia with low RD (Ongur et al. 2005). MDD patients with comorbid axis II disorder have been associated with high HA and also with somewhat high NS (Battaglia et al. 1996).

4.5.4 Temperament and personality dimensions as possible endophenotypes for MDD

The term endophenotype has been described as an internal, measurable component unseen by the unaided eye along the pathway between disease and distal genotype (Gottesman and Gould 2003). Most often endophenotypes are used in genetic analysis of disease, but also in diagnosis and classification (Gottesman and Gould 2003). An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological (including configured self-report data) in nature (Gottesman and Gould 2003). It has been suggested that an endophenotype for psychiatric disorder has to meet certain criteria, including specificity (the endophenotype is more strongly associated with the disease of interest than with other psychiatric conditions), state-independence, heritability, family association, cosegregation (the endophenotype is more prevalent among the ill relatives of ill probands compared with the well relatives of the ill probands) and biological and clinical plausibility (Tsuang et al. 1993). Several putative endophenotypes for MDD have been suggested, including anhedonia-related endophenotypes, like RD; and increased stress sensitivity - related endophenotypes, like HA and N (Hasler et al. 2004).

4.6 A conclusion of previous literature

Although several studies have investigated the associations between personality dimensions and the symptoms of depression and anxiety, there are also several limitations in these studies. Only few (Bienvenu et al. 2004; Cox et al. 2004) studies have been undertaken in the general population to explore the association between neuroticism and extraversion and symptoms of anxiety and depression and none have explored anxiety with both dimensions. Moreover, although a few published studies have employed the revised version of TCI (Lindgren 2002; Gutierrez-Zotes et al. 2004; Hansenne et al. 2005; Pelissolo et al. 2005; Fossati et al. 2007), none have explored the association between the dimensions of TCI-R and symptoms of depression and anxiety in the adult general population.

The view that high neuroticism is a risk factor for depression has been supported mainly by prospective epidemiological studies (Kendler et al. 2002, 2006 a, c; Ormel et al. 2004). However, the extent to which the findings of an epidemiological study can be generalized to clinical samples is often uncertain, as compared to subjects of an epidemiological study; patients from clinical samples tend to have more severe, long-lasting and recurrent depressive episodes, commonly comorbid with personality disorders. There are few premorbidly started clinical studies conducted among primiparous women (Boyce et al. 1991), family members of patients with depression (Hirschfeld et al. 1989; Shea et al. 1996) and car owners (Nyström and Lindegård 1975) or male conscripts (Angst and Clayton 1986) with neuroticism-like traits, but none among depressed patients from the general population. Moreover, the role of extraversion is more obscure than that

of neuroticism, as extraversion has been found to be (Hirschfeld et al. 1983a; Kendler et al. 2006a) or not to be (Angst and Clayton 1986; Hirschfeld et al. 1989) a risk factor for depression. There are also contradictory findings, whether the scores of neuroticism and extraversion change (Hirschfeld et al. 1989) or not (Shea et al. 1996; Ormel et al. 2004) after an episode of depression. Finally, the state of anxiety, which also might influence the scores of neuroticism (Bienvenu et al. 2001; Cuijpers et al. 2005) and of extraversion (Reich et al. 1986) has only rarely (Reich et al. 1987) been explicitly controlled.

In the former studies, the information on the associations between neuroticism and extraversion and axis I or II comorbid disorders among patients with MDD has been fragmentary. Knowledge of this comorbidity derives mostly from studies exploring MDD and either comorbid axis I or II disorders separately, but not both axes concurrently. Moreover, only one earlier study of MDD and comorbid disorders, evaluating MDD and comorbid general anxiety disorder (GAD) (Kendler et al. 2007), has been longitudinal and controlled for the possible confounding state-effect of depression. Little is also known about whether the levels of neuroticism and extraversion differ between patients with pure MDD and those with comorbid axis I or II disorder.

5. AIMS OF THE STUDY

This study investigated the relationship between the TCI dimensions, neuroticism and extraversion and symptoms of depression and anxiety among 441 participants from the general population survey, and also between neuroticism and extraversion and MDD in a cohort of 193 secondary level care MDD patients as compared with the general population.

The specific aims of the study were as follows:

I To investigate among the general population, 1) whether Harm Avoidance would have a positive and Self-Directedness a negative correlation with both depressive and anxiety symptoms, 2) whether these dimensions would predict the use of health care services for mental disorders, and 3) whether Harm Avoidance but not Self-Directedness would be associated with self-reported family history of mental disorders.

II To investigate among the general population, 1) whether neuroticism would have a positive and extraversion a negative correlation with depressive and anxiety symptoms, and 2) whether both dimensions would be related to the use of health care services for psychiatric reasons.

III To investigate, 1) whether neuroticism and extraversion would be affected by depression (the 'state effect'), 2) and/or be shaped by the recurrence or relapse of depressive episodes (the 'scar effect') and finally, 3) whether these dimensions would act as risk factors for depression ('trait effect').

IV To investigate among MDD patients, 1) whether a dose-exposure relationship would exist between standardized levels of neuroticism and extraversion and the type and number of comorbid axis I and II disorders, and 2) to investigate the standardized scores of neuroticism and extraversion among pure MDD and with comorbid axis I or II disorders.

6. METHODS

6.1 General study design

This study is part of the Mood Disorders Project conducted by the Department of Mental Health and Alcohol Research, National Public Health Institute. The general population survey study was conducted in 2003 in two adjacent cities of Espoo and Vantaa, combined population 408 270 in 2003. The Vantaa Depression Study (VDS) is a collaborative depression research project between the Department of Mental Health and Alcohol Research of the National Public Health Institute and the Department of Psychiatry of the Peijas Medical Care District (PMCD). Vantaa is the fourth largest city in Finland, with a population of 169 000 in 1997, and provides psychiatric services to all of its citizens free of charge. The research protocol for the general population survey study was approved by the Ethics Committee of Helsinki University Central Hospital, and that for VDS by the Ethics Committee of the PMCD.

Due to the study design, the publications had different general population survey samples and MDD patient compositions as presented in Table 6.

Table 6. Composition of general population survey samples and MDD patient cohort in the original publications.

	Genaral population survey	**Vantaa Depression Study**
Study I	Participants, who returned the whole questionnaire, N=347	
Study II	Participants, who returned the whole questionnaire and the shortened version of it, N=441	
Study III	Participants aged 20-60 years, N=388	Patients followed up at both 6 and 18 months, remained unipolar, N=193
Study IV	Participants aged 20-60 years, N=388	Patients followed up at both 6 and 18 months, remained unipolar, N=193

6.2 General population survey

A random sample of 900 subjects (300 from Espoo, 600 from Vantaa) was randomly drawn from the National Population Register Centre. Each was mailed a self-report booklet that included sociodemographic characteristics and, among other measures, the 21-item Beck Anxiety Inventory, (BAI, Beck et al. 1988b); the 21-item Beck Depression Inventory (BDI, Beck et al. 1961); the 240-item Temperament and Character Inventory-Revised (TCI-R, Cloninger 1994); the 57-item Eysenck Personality Inventory (EPI-form B, Eysenck and Eysenck 1964) and additional questions on whether a physician had ever diagnosed a mental disorder, the respondent had used health services for a mental health problem during the past 12 months, or if a mental disorder had been diagnosed in relatives. Written informed consent was obtained from all participants after details of the study were described.

Due to the design of the Mood Disorders Project, participants from Espoo were 20-60 years old and from Vantaa 20-70 years. After three weeks, the questionnaire was mailed again to non-responders. Finally, a shortened version (without TCI-R) was sent to those who had still failed to respond. Of the 441 responders, 347 returned the whole questionnaire and 94 only the shortened version, no sociodemographic differences existed between the first and second mailing groups. Non-responders were younger than responders (mean age 41.4 years, sd 12.5 vs. 45.0 years, sd 12.5, t=-4.387, $p<0.001$) and were more often male (62.3% vs. 48.8%, $\chi^2=16.7487$, df=1, $p<0.001$), but no difference was present in the area of residence within the city. Responders differed slightly from the age-matched general population of the same area. They were older (45.0 years vs. 40.7 years, $\chi^2=27.5374$, df=7, $p=0.001$), more often married or cohabiting (married or cohabiting 60.6% vs. 49.5%, single 18.2% vs. 36.8%, divorced 18.5% vs. 12.2%, widowed 2.7% vs. 1.5%, $\chi^2=2.71$, df=3, $p<0.001$), more often employed (employed 86.8% vs. 78.7%, student 4.2% vs. 7.8%, unemployed 5.3% vs. 4.9%, pensioned 7.9% vs. 8.5%, $\chi^2=60.9139$, df=4, $p<0.001$) and had a slightly higher level of education (university degree 17.3% vs. 20.1%, polytechnic or equivalent degree 34.9% vs. 15.8%, vocational education 25.4% vs. 39.4%, no professional education 22.4% vs. 24.7%, $\chi^2=114.854$, df=3, $p<0.001$). No gender difference was present.

Studies III and IV included only participants aged 20-60 years (N=816). In this age group no sociodemographic differences existed between the first and second mailing groups. Non-responders were younger than responders (mean age 39.6 years, sd 10.8 vs. 42.7 years, sd 11.0, t=-3.126, $p<0.001$) and were more often male (58.3% vs. 48.5%, $\chi^2=16.12$, df=1, $p<0.001$), but no difference was present in the area of residence within the city. Responders differed slightly from the age-matched general population of the same area.

They were somewhat older (42.7 years vs. 39.8 years, χ^2=18.35, df=4, p<0.01), differed in marital status (married or cohabiting 60.6% vs. 49.7%, single 19.4% vs. 36.9%, divorced 18.1% vs. 12.4%, widowed 1.8% vs. 1.0%, χ^2=53.88, df=3, p<0.001) and had a slightly higher level of education overall (university degree 17.3% vs. 19.0%, polytechnic or equivalent degree 36.4% vs. 26.4%, vocational education 25.4% vs. 29.5%, no professional education 20.9% vs. 22.0%, χ^2=16.51, df=3, p<0.001). No gender or work status difference was present.

The sociodemographic characteristics of the respondents of the general population survey in study I and II are shown in Table 7, and in study III and IV in Table 8.

6.3 MDD patient cohort

6.3.1 Screening

The first phase of patient sampling for the VDS involved screening all patients aged 20-60 years (N=806) in the PMCD for a possible new episode of DSM-IV MDD between 1 February 1997 and 31 May 1998 (Melartin et al. 2002). During that period, all patients (N=806) aged 20-59 years, who were 1) seeking treatment at, 2) being referred to, or 3) already receiving care and currently showing signs of deteriorating clinical state in the Department of Psychiatry, but without a clinical diagnosis of ICD-10 schizophrenia or bipolar I disorder, were screened for the presence of depressive symptoms. The screening instrument included the five screening questions regarding depression from the WHO Schedules for Clinical Assessment in Neuropsychiatry (SCAN), version 2.0 (Wing et al. 1990). The Scale for Suicidal Ideation (SSI, Beck et al. 1979b) was also completed in order to disclose the individuals with moderate to severe suicidal ideation plans. If the following criteria matched the patients after either 1) a positive response to any of the SCAN screening questions, 2) clinical suspicion of depression by the interviewing personnel, or 3) a score of six or more in the SSI irrespective of any depressive symptoms, she/he was fully informed about the study project and her/his participation requested. Of the 703 eligible patients, 542 (77.1%) agreed and gave their written informed consent. The non-participating did not differ significantly (p>0.05) in age or gender from those who consented.

6.3.2 Baseline evaluation

6.3.2.1 Diagnostic measures

In the second phase, a researcher using SCAN 2.0 (Wing et al. 1990) interviewed the 542 consenting patients. Patients were examined whether or not the current mood episode fulfilled the criteria for DSM-IV MDD, using also melancholic and atypical features specifiers. All psychiatric and medical records in the PMCD, including a standardized set of laboratory test, were also available at the interview. Patients with current alcohol or

other substance abuse were interviewed after two or three weeks of abstinence, in order to eliminate substance-induced mood disorders. On this basis, 269 of the 542 patients were subsequently diagnosed with DSM-IV MDD and included in the study. The diagnostic reliability of SCAN 2.0 was excellent (κ=0.86, 95% CI 0.58-1.0) (Melartin et al. 2002).

The researcher made the decision during the interview whether or not to include the patient in the study, after which an entire SCAN interview was conducted to achieve a full picture of Axis I comorbid disorders. In addition, the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II)(Spitzer et al. 1989) was used to assess diagnoses on Axis II.

6.3.2.2 Exclusion criteria

Patients with a diagnosis of DSM-IV bipolar I or II disorder, organic or substance-induced mood disorder, schizoaffective disorder, schizophrenia or another non-affective psychosis were excluded from the study, even if they fulfilled the symptom criteria of current MDE. Excluded were also the cases with a history of MDD if the current episode did not fulfill the criteria of the disorder.

6.3.2.3 Observer and self-report scales

The cohort baseline measurements included among the other observer scales: 17-item Hamilton Rating Scale for Depression (HAM-D, Hamilton 1960) to assess the severity of depression and Social and Occupational Functioning Assessment Scale of DSM-IV (SOFAS, Goldman et al. 1992) to assess the level of functioning.

The self-report scales included among other scales the 57-item Eysenck Personality Inventory (EPI form B, Eysenck and Eysenck 1964) for neuroticism and extraversion, the 21-item Beck Depression Inventory (BDI, Beck et al. 1961) for the severity of depression and the 21-item Beck Anxiety Inventory (BAI, Beck et al. 1988b) for the level of anxiety.

6.3.3 Follow-up procedure

Of the 269 individuals with a current MDD initially included in the study, 193 could be followed up at both 6 and 18 months, and their depression had remained unipolar (the diagnosis switched to bipolar in 13/269 patients, 5%) (Melartin et al. 2004). Patients who dropped out from the follow-up were younger (36.1 years, sd 10.1 vs. 41.0 years, sd 11.1, t=-3.352, p=0.001) and had scored slightly higher on the baseline BAI scale (24.4, sd 10.6 vs. 21.5, sd 10.6, t=-2.055, p=0.04), but did not differ significantly (p>0.05) in other sociodemographic variables or in BDI, neuroticism or extraversion scales. The majority (170/193, 88.1%) were receiving antidepressants at normal adult doses.

6.3.3.1 Outcome measures, personality dimensions and life-chart methodology

The outcome of MDD was investigated at 6 and 18 months by repeated SCAN 2.0 interviews, observer- and self-report scales, including the life-chart, the HAM-D, the BAI, and the BDI and medical and psychiatric records. The personality dimensions of neuroticism and extraversion were evaluated at 6 and 18 months by the EPI.

A detailed life-chart was created based on DSM-IV criteria and definitions. Time after the first baseline interview was divided into three periods: state of full remission (none of the 9 MDE criteria symptoms), state of partial remission (1-4 of the 9 symptoms) or state of MDE (5> of the 9 symptoms). Recurrence was defined as a return of symptoms after at least two consecutive months of partial or full remission, and relapse as a return of symptoms fulfilling criteria for major depressive episode (MDE), following a period with symptoms below the MDE threshold of less than two months.

The sociodemographic characteristics of the patients of the VDS cohort are shown in Table 8.

6.4 Statistical methods

Several parametric and non-parametric statistical methods were used. Univariate analyses included Student's t-test, Pearson's chi-square test, one-way analysis of variance (ANOVA), Mann-Whitney test, Kruskal-Wallis test, Pearson's correlation coefficient, Spearman's rho (r_s) and Fisher's exact test. Cronbach's alpha was applied to assess internal consistency. SPSS software, version 11.5, was used.

6.4.1 Study I and II

In the first and second study, two multiple regression analyses were performed, one with BDI (scores divided into six categories: 0, 1 to 4, 5 to 9, 10 to 16, 17 to 29, and 30 to 63) and one with BAI (scores divided into six categories: 0, 1 to 4, 5 to 9, 10 to 18, 19 to 29 and 30 to 63) as dependent factor, and gender, age, education and the seven TCI dimensions (in the first study) or neuroticism and extraversion (in the second study) as independent factors. The BDI and BAI scores were transformed because of the skewness of their distribution.

6.4.2 Study III

In the third study to examine the 'state effect', the scores of neuroticism and extraversion were compared between three different time points (baseline, 6 months and 18 months). To investigate whether the scores of neuroticism and extraversion would change after an episode of depression, the 'scar effect', a subgroup of patients were separated who had a recurrence or relapse(s) of depression between, but not at, the 6- and 18-month

follow-ups and compared the scores of neuroticism and extraversion at these two time points. To examine the 'trait effect', of each subject in the VDS cohort, was determined at an index interview (at baseline or at the 6-month or 18-month follow-up), conducted when the HAM-D scores were at a minimum. The scores of neuroticism and extraversion from the index interview were then compared with scores for the total general population group and also with the no self-reported lifetime mental disorder group.

Several multiple regression analyses were performed to investigate the 'state effect' and the 'trait effect', all including age, gender, education, marital status and work status as independent variables or covariates. In addition, BDI and BAI change scores (18-month follow-up and baseline) and either baseline neuroticism or extraversion scores, were also included as independent variables in the final linear regression model to investigate the 'state effect', with 18-month follow-up, neuroticism and extraversion as a dependent variable. BDI, BAI, neuroticism and extraversion scores (baseline score from the no self-reported lifetime mental disorder general population group and index interview score from the VDS cohort) also served as covariates in the final logistic regression model to investigate the 'trait effect'; belonging to the VDS cohort, the general population or the self-reported lifetime mental disorder group served as the dependent variable. To estimate which dependent variable of the regression model investigating the 'state effect' contributed the most, the part correlation coefficients were squared to get the partial R-squares. All the tests were made also separately for females and males.

6.4.3 Study IV

In the fourth study among VDS patients, an axis I comorbid diagnoses assigned at any time point (baseline or 6-month or 18-month follow-up) by SCAN 2.0 (Wing et al. 1990) was included in the analysis. For axis II diagnoses, an index interview (baseline or 6-month or 18-month follow-up), conducted when the HAM-D scores were at a minimum (mean±SD was 5.7±5.7), was determined. Personality disorder diagnoses made at this time point were used in the analysis.

To investigate the prevalence of a comorbid axis I or II disorder (categorical), specifiers of MDD and SOFAS (Social and Occupational Functioning Scale) in VDS patients by different levels of neuroticism and extraversion of the general population, the scores of neuroticism from the general population were divided into four levels [very high (> +2 sd), high (from +1 - +2 sd), normal (from -1 sd - +1 sd) and low (< -1 sd)] as well as the scores of extraversion [high (> +1 sd), normal (from -1 sd - +1 sd), low (< -1 sd- > -2 sd) and very low (<-2 sd)].

Several multiple linear and logistic regression analyses were performed to investigate the relationship of neuroticism and extraversion to the comorbidity of MDD with axis I and/or

II disorders, all including age, gender, HAM-D and either the scores of neuroticism or extraversion or both as independent variables or covariates, with the number of positive items of each personality disorder or whether or not axis I or II disorder was present as a dependent variable.

To compare the level of neuroticism and extraversion between patients with pure MDD or with comorbid axis I or II disorders, the mean scores of neuroticism and extraversion of the depressive patients were converted into standardized scores (Z-scores), the mean score of neuroticism and extraversion from the general population being zero.

Table 7. Sociodemographic characteristics of the general population sample for the study I (N=441) and study II (N=347).

	Female		Male		Total	
Characteristic	**Study I** N (%)	**Study II** N (%)	**Study I** N (%)	**Study II** N (%)	**Study I** N (%)	**Study II** N (%)
Total	226 (51.2)	184 (53.0)	215 (48.8)	163 (47.0)	441 (100)	347 (100)
Marital status[a]						
Single	42 (18.7)	32 (17.4)	38 (17.8)	26 (16.0)	80 (18.2)	58 (16.7)
Cohabiting	37 (16.4)	31 (16.8)	47 (22.0)	34 (20.8)	84 (19.1)	65 (18.7)
Married	86 (38.2)	71 (38.6)	96 (44.9)	75 (46.0)	182 (41.5)	146 (42.1)
Divorced	54 (24.0)	44 (23.9)	27 (12.6)	22 (13.5)	81 (18.5)	66 (19.0)
Widowed	6 (2.7)	6 (3.3)	6 (2.8)	6 (3.7)	12 (2.7)	12 (3.5)
Education[b]						
University	40 (17.9)	33 (18.1)	35 (16.7)	25 (15.7)	75 (17.3)	58 (17.0)
Polytechnic or equivalent	89 (39.7)	73 (40.1)	62 (29.7)	51 (32.1)	151 (34.9)	124 (36.4)
Vocational school	38 (17.0)	33 (18.1)	72 (34.4)	55 (34.6)	110 (25.4)	88 (25.8)
No professional education	57 (25.4)	43 (23.7)	40 (19.1)	28 (17.6)	97 (22.4)	71 (20.8)
Work status[c]						
Employed	195 (88.3)	160 (87.5)	180 (85.3)	126 (78.7)	375 (86.8)	286 (83.4)
Student	9 (4.1)	7 (3.8)	9 (4.3)	6 (3.8)	18 (4.2)	13 (3.8)
Unemployed	11 (5.0)	7 (3.8)	12 (5.7)	9 (5.6)	23 (5.3)	16 (4.7)
Disability pension	12 (5.4)	9 (4.9)	22 (10.4)	19 (11.9)	34 (7.9)	28 (8.1)
Self-reported mental disorder, lifetime[d]	38 (16.8)	31 (16.8)	19 (8.8)	15 (9.2)	57 (12.9)	46 (13.3)
Self-reported contact with health care for psychiatric reason in last 12 months	26 (11.6)	21 (11.5)	15 (7.0)	10 (6.1)	41 (9.4)	31 (9.0)
Family history of mental disorder[e]	82 (36.6)	69 (37.9)	35 (16.6)	28 (17.4)	117 (26.9)	97 (28.3)
First degree[f]	50 (22.1)	40 (21.7)	21 (9.8)	16 (9.8)	71 (16.1)	56 (16.1)
Spouse	6 (2.7)	5 (2.7)	3 (1.4)	3 (1.8)	9 (2.0)	8 (2.3)
Other relative[g]	32 (14.2)	31 (16.8)	11 (5.1)	9 (5.5)	43 (9.8)	40 (11.5)
Age (years)	Mean (sd) 44.9 (12.4)	Mean (sd) 44.0 (12.6)	Mean (sd) 45.2 (12.6)	Mean (sd) 45.7 (12.8)	Mean (sd) 45.0 (12.5)	Mean (sd) 44.8 (12.8)

Study I
[a] χ^2=10.671, df=4, p=0.031, missing data 2/441
[b] χ^2=18.151, df=3, p<0.001, missing data 8/441
[d] χ^2=6.229, df=1, p=0.013
[e] χ^2=22.147, df=1, p<0.001, missing data 6/441
[f] χ^2=12.454, df=1, p<0.001
[g] χ^2=10.239, df=1, p=0.001

Study II
[b] missing data 6/347
[c] missing data 4/347
[d] χ^2=4.393, df=1, p=0.036
[e] χ^2=17.737, df=1, p<0.001
[f] χ^2=9.079, df=1, p=0.003
[g] χ^2=10.872, df=1, p=0.001

Table 8. Sociodemographic characteristics of a general population sample (N=388), total and divided by self-reported lifetime mental disorder, and unipolar depressive patients in the Vantaa Depression Study (N=193).

	General population, no self-reported lifetime mental disorder (N=338)		General population self-reported lifetime mental disorder (N=50)		General population, total (N=388)		MDD patients (N=193)	
Characteristic	N	(%)	N	(%)	N	(%)	N	(%)
Gender[a1,a2]								
Female	167	49.4	33	66.0	200	51.5	139	72.0
Male	171	50.6	17	34.0	188	48.5	54	28.0
Marital status[b1,b2]								
Single	63	18.8	12	24.0	75	19.4	38	19.7
Cohabiting	71	21.0	7	14.0	78	20.2	35	18.1
Married	142	42.3	14	28.0	156	40.4	69	35.8
Divorced	54	16.1	16	32.0	70	18.1	44	22.8
Widowed	6	1.8	1	2.0	7	1.8	7	3.6
Education[c1,c2]								
University	61	18.3	5	10.4	66	17.3	17	8.8
Polytechnic	123	36.8	16	33.3	139	36.4	53	27.5
Vocational school	80	24.0	17	35.4	97	25.4	45	23.3
No professional education	70	21.0	10	20.8	80	20.9	78	40.4
Work status[d1,d2]								
Employed	294	87.2	38	76.0	332	85.8	129	68.6
Student	16	4.7	2	4.0	18	4.7	16	8.5
Unemployed	18	5.3	2	4.0	20	5.2	34	18.1
Pensioned, psychiatric reason	0	0	5	10.0	5	1.3	7	3.7
Pensioned, somatic reaseon	9	2.7	3	6.0	12	3.1	2	1.1
	Mean	sd	Mean	sd	Mean	sd	Mean	sd
Age, years	42.7	11.0	42.3	11.1	42.7	11.0	41.0	11.1

Significance: no self-reported lifetime mental disorder vs. self-reported lifetime mental disorder
a[1] χ^2= 4.801, df=1, p=0.028
b[1] χ^2= 10.003, df=4, p=0.04, missing data 2/338
c[1] missing data 4/338, 2/50
d[1] χ^2= 36.102, df=4, p<0.001, missing data 1/338

Significance: normal population vs. unipolar depressive patients
a[2] χ^2=22.232, df=1, p<0.001
b[2] missing data 2/388
c[2] χ^2=27.347, df=3, p<0.001, missing data 6/388
d[2] χ^2=36.062, df=4, p<0.001, missing data 1/388, 5/193

7. RESULTS

7.1 The dimensions of temperament and character and symptoms of anxiety and depression in the general population

7.1.1 Mean scores and Cronbach's alphas of TCI-R, BDI and BAI

The mean scores on most of the dimensions were lower in men than in women; they scored lower on NS, HA, RD, C, ST, BDI and BAI. Women had lower scores on P, and no difference was found on SD. The mean scores, standard deviations and Cronbach's alphas are shown in Table 9.

Table 9. Mean scores and standard deviations on the TCI-R, BDI and BAI. Comparisons between genders, and Cronbach's alpha coefficients (N=347).

TCI-R	Female mean ± sd	Male mean ± sd	Total mean ± sd	α	t	p
NS[a]	102.7 ± 17.6	97.9 ± 14.5	100.5 ± 16.4	0.85	2.703	0.007
HA[a]	92.9 ± 20.8	84.9 ± 17.8	89.2 ± 19.8	0.89	3.809	<0.001
RD[b]	107.8 ± 13.7	95.9 ± 13.7	102.3 ± 14.9	0.86	7.984	<0.001
P[b]	112.9 ± 16.8	116.6 ± 17.6	114.6 ± 17.3	0.89	-2.027	0.043
SD[b]	146.5 ± 19.1	147.2 ± 16.9	146.8 ± 18.1	0.87		ns
C[a]	140.5 ± 13.1	133.0 ± 15.6	137.0 ± 14.8	0.86	4.827	<0.001
BDI[b,d]	7.11 ± 8.93	4.64 ± 5.45	5.95 ± 7.60	0.92	3.635	0.003
BAI[a,e]	7.42 ± 8.28	5.49 ± 6.91	6.51 ± 7.72	0.91	2.323	0.021

[a] missing data 4/347
[b] missing data 5/347
[c] missing data 8/347
[d] Mann-Whitney U=12408.5, Z=-2.372, p=0.018
[e] Mann-Whitney U=12252.5, Z=-2.628, p=0.009

TCI-R=Temperament and Character Inventory-Revised,
NS=Novelty Seeking, HA=Harm Avoidance, RD=Reward Dependence, P=Persistance, SD=Self-Directedness, C=Co-operativeness, BDI=Beck Depression Inventory, BAI=Beck Anxiety Inventory

7.1.2 Symptoms of anxiety

Most of the responders had no or only low levels of anxiety. The range of scores on the BAI was 0 to 50, median 4.0, and the distribution was skewed to the left. When subdividing the scores into four categories, 76.4% of respondents had no anxiety (scores 0-9), 15.5% had mild anxiety symptoms (10-18), 5.8% moderate anxiety symptoms (19-29) and 2.3% severe anxiety symptoms (30-63).

7.1.3 Symptoms of depression

The level of deprssion was also low among the individuals of the sample. The scores on the BDI ranged from 0 to 51, median 3.0, and the distribution was again highly skewed to the left. After the scores of the whole sample were subdivided into four categories 77.8% of respondents were not depressed (scores 0-9), 15.2% had mild depressive symptoms (10-16), 5.3% moderate depressive symptoms (17-29) and 1.8% severe depressive symptoms (30-63).

7.1.4 Correlations of the BDI, BAI and TCI-R

The scores on the BDI correlated most negatively with SD (r_s=-0.495, p<0.001) and most positively with HA (r_s=0.555, p<0.001). Scores on the BAI also correlated most negatively with SD (r_s=-0.458, p<0.001) and most positively with HA (r_s=0.560, p<0.001). The scores of the BDI correlated also with the other dimensions of the TCI-R: NS r_s=-0.145, (p=0.007), RD r_s=-0.170, (p=0.002), P r_s=-0.154, (p=0.005), C r_s=-0.184, (p=0.001) and ST r_s=0.096, (p=ns). The correlations between the scores on the BAI and other dimensions of TCI-R were: NS r_s=-0.063, (p=ns), RD r_s=-0.143, (p=0.008), P r_s=-0.136, (p=0.012), C r_s=-0.214, (p<0.001) and ST r_s=0.172, (p=0.002). Age correlated significantly with NS (r=-0.344, p<0.001), RD (r=-0.169, p=0.002) and HA (r=0.133, p=0.036). The correlation between the BDI and BAI scores was strong, r_s=0.726 (p<0.001). The correlations between the dimensions of TCI-R were moderate.

7.1.5 Health related questions

Health care use due to a mental health problems (self-reported) during the past year correlated with HA (r_s=0.241, p<0.001), P (r_s=-0.148, p=0.006), SD (r_s=-0.135, p=0.013), and the BDI (r_s=0.288, p<0.001) and BAI (r_s=0.289, p<0.001) scores.

Family history of mental disorder (self-reported) in a first-degree relative correlated with HA r_s=0.202, (p<0.001), P r_s=-0.143, (p=0.008), and BDI r_s=0.145, (p=0.007) and BAI r_s=0.139, (p=0.01) scores. However, there was no correlation with SD (r_s=0.019, p=ns).

Lifetime mental disorder (self-reported) correlated significantly with scores on the BDI (r_s=0.239, p<0.001), BAI (r_s=0.194, p<0.001), HA (r_s=0.272, p<0.001), P (r_s=-0.209, p<0.001) and SD (r_s=-0.225, p<0.001).

7.1.6 Multivariate models

In multiple regression models with BDI and BAI scores as dependent variables, and HA, P, SD, ST, age, education and gender as independent variables, BDI appeared to significantly associate only with HA (β=0.511, t=8.160, p<0.001) and SD (β=-0.206, t=-3.629, p<0.001), whereas BAI associated with HA (β=0.534, t=8.321, p<0.001), SD (β=-0.144, t=-2.484, p=0.013) and unexpectedly also with P (β=0.124, t=2.437, p=0.015) and ST (β=0.143, t=3.097, p=0.002).

7.2 Neuroticism and extraversion and symptoms of anxiety and depression in the general population

7.2.1 Mean scores and Cronbach's alphas of EPI, BDI and BAI

The mean scores of most of the dimensions were lower in men than in women. Men scored lower on neuroticism, liability, BDI and BAI, but no difference was found on extraversion. The mean scores, standard deviations and Cronbach's alphas are shown in Table 10.

Table 10. Mean scores and standard deviations on the EPI, BDI and BAI. Comparisons between genders, and Cronbach's alpha coefficients (N=441).

EPI	Female mean ± sd	Male mean ± sd	Total mean ± sd	α	Mann-Whitney U-test	p
N[ab]	10.18 ± 5.05	8.48 ± 5.22	9.35 ± 5.20	0.85		0.001
E[c]	13.38 ± 4.64	13.20 ± 4.40	13.29 ± 4.52	0.79		ns
Lie[a]	2.05 ± 1.52	1.55 ± 1.51	1.81 ± 1.54	0.50	U=18814.0 Z=-3.907	<0.001
BDI[b]	6.79 ± 8.44	4.77 ± 5.93	5.76 ± 7.38	0.93	U=20619.5 Z=-2.329	0.017
BAI[b]	7.08 ± 8.04	5.53 ± 7.35	6.32 ± 7.75	0.91	U=20268.5 Z=-2.656	0.008

[a] Missing data 4/441
[b] Student's t-test=4.471
[c] Missing data 5/441

EPI=Eysenck Personality Inventory,
N=Neuroticism, E=Extraversion,
BDI=Beck Depression Inventory, BAI=Beck Anxiety Inventory

7.2.2 Symptoms of anxiety

The level of anxiety was also low among participants. BAI scores ranged from 0 to 50, the median being 4.0 and the distribution was skewed to the left. Upon subdividing the scores into four categories, 77.5% of respondents had no anxiety (score 0-9), 13.3% had mild anxiety symptoms (score 10-18), 6.7% moderate anxiety symptoms (score 19-29) and 2.5% severe anxiety symptoms (score 30-63).

7.2.3 Symptoms of depression

Most of the respondents had no or only a low level of depression. BDI scores ranged from 0 to 51, the median being 3.0 and the distribution was highly skewed to the left. After scores of the entire sample were subdivided into four categories, 78.4% of respondents were not depressed (score 0-9) 15.4% had mild depressive symptoms (score 10-16), 4.4% moderate depressive symptoms (score 17-29) and 1.8% severe depressive symptoms (score 30-63).

7.2.4 Correlations of BDI, BAI and EPI

The correlation between BDI and BAI scores was strong (r_s=0.727, p<0.001). N scores correlated positively with BDI (r_s=0.714, p<0.001) and BAI (r_s=0.694, p<0.001) scores, whereas E scores correlated negatively with both BDI (r_s=-0.473, p<0.001) and BAI (r_s=-0.362, p<0.001) scores. N scores correlated negatively with E scores (r_s=-0.442, p<0.001). Scores on the lie scale correlated somewhat with BDI scores (r_s=0.104, p=0.03) and E scores (r_s=-0.155, p=0.001), but not with BAI scores (r_s=0.092, p=ns) or N scores (r_s=-0.003, p=ns).

7.2.5 Health related questions and age

Lifetime mental disorder (self-reported) correlated significantly with the scores of BDI (r_s=0.251, p<0.001), BAI (r_s=0.210, p<0.001), N (r_s=0.299, p<0.001) and E (r_s=-0.168, p<0.001). Health care use due to mental health problems (self-reported) during the past year correlated with N scores (r_s=0.235, p<0.001), E (r_s=-0.137, p=0.004), BDI (r_s=0.281, p<0.001) and BAI (r_s=0.288, p<0.001). Family history of mental disorder in first-degree relatives (self-reported) correlated with N scores (r_s=0.101, p=0.034), BDI (r_s=0.128, p=0.007) and BAI (r_s=0.145, p=0.01), as well as with health care use for mental health problems (self-reported) during the past year (r_s=0.180, p<0.001) and self-reported lifetime mental disorder (r_s=0.273, p<0.001). Age correlated negatively with E scores (r=-0.248, p<0.001) and positively with scores on the lie scale (r=0.193, p=0.001), but not significantly with N scores (r=-0.37, p=ns). The correlation between age and BDI scores was modest (r_s=0.118, p=0.014).

7.2.6 Multivariate models

In multiple regression models with BDI and BAI scores as dependent variables, and N, E, gender, age and education as independent variables, BDI appeared to be significantly associated with N (β=0.624, t=16.059, p<0.001), E (β=-0.176, t=-4.479, p<0.001) and age (β=0.095, t=2.712, p=0.007), whereas BAI was associated only with N (β=0.676, t=16.361, p<0.001).

7.3 Neuroticism, extraversion and MDD

7.3.1 Mean scores of neuroticism and extraversion

N scores declined and E scores increased during the follow-up period of MDD patients. After a relapse or recurrence of depressive disorder, both of these scores remained at the same level than before the episode. Mean scores of N were higher and those of E lower in the MDD patient group than in the general population. The mean scores and standard deviations are shown in Table 11.

7.3.2 Comparisons for the 'state effect'

7.3.2.1 Neuroticism and extraversion scales and gender

During the 18-month follow-up period N scores decreased (mean 17.2, sd 3.7 vs. 13.7, sd 5.6, t=10.034, p<0.001) and E scores increased (mean 10.0, sd 4.7 vs. 11.2, sd 4.5, t=-5.078, p<0.001) significantly. No significant differences were observed between men and women.

7.3.2.2 Neuroticism and extraversion scales and BDI and BAI scores

The positive correlation between BDI scores and N increased during the follow-up (baseline: r_s=0.267, p<0.001; 6-month follow-up: r_s=0.587, p<0.001; 18-month follow-up: r_s=0.688, p<0.001), as well as the negative correlation between BDI scores and E (baseline: r_s=-0.152, p<0.05; 6-month follow-up: r_s=-0.434, p<0.001; 18-month follow-up: r_s=-0.433, p<0.001). In addition, the positive correlation between BAI scores and N increased (baseline: r_s=0.375, p<0.001; 6 months: r_s=0.701, p<0.001; 18 months: r_s=0.713, p<0.001) as also somewhat the negative correlation between BAI scores and E (baseline: r_s=-0.165, p<0.05; 6 months: r_s=-0.403, p<0.001; 18 months: r_s=-0.298, p<0.001).

Table 11. Mean scores and standard deviations on BDI, BAI, neuroticism and extraversion of a general population sample (N=388), total and divided by self-reported lifetime mental disorder, and unipolar depressive patients. Comparisons between groups and Cronbach's alpha coefficients (N=193).

	(I) General population, no self-reported lifetime mental disorder (N=338)			(II) General population, self-reported lifetime mental disorder (N=50)			(III) General population, total (N=388)			(IV) Unipolar depressive patients (N=193)			ANOVA[a] I vs. II vs. IV	Singificance[b] III vs. IV
Characteristic	Mean	sd	α	Mean	sd	α	Mean	sd	α	Mean	sd	α	F	t
BDI														
Baseline[c]	4.6	5.4	0.91	13.3	13.2	0.92	5.7	7.5	0.92	27.3	8.2	0.81	581.378*** (I<II<IV)#	34.999***
6 months										12.6	9.6	0.92	74.659*** (I<II,IV)#	11.103***
18 months										11.1	10.0	0.93	53.288*** (I<II,IV)#	8.716***
At index interview[h]										9.7	9.3		43.939*** (I<IV<II)#	5.582***
BAI														
Baseline[d]	5.6	6.4	0.90	12.6	12.7	0.92	6.5	7.9	0.91	21.5	10.6	0.89	204.181*** (I<II<IV)#	20.816***
6 months										13.2	9.8	0.91	56.435*** (I<II,IV)#	10.37***
18 months										11.5	10.3	0.93	36.985*** (I<II,IV)#	7.911***
At index interview[h]										10.7	9.5		32.029*** (I<IV<II)#	5.623***
Neuroticism														
Baseline[e]	8.7	5.0	0.85	13.8	4.8	0.87	9.4	5.2	0.86	17.2	3.7	0.73	207.575*** (I<II<IV)#	19.501***
6 months[f]										14.7	5.3	0.85	93.143*** (I<II,IV)#	12.47***
18 months										13.7	5.6	0.87	65.685*** (I<II,IV)#	10.059***
At index interview[h]										13.7	5.5		65.230*** (I<II,IV)#	9.073***
Extraversion														
Baseline[g]	13.9	4.4	0.79	11.3	5.0	0.76	13.5	4.5	0.79	10.0	4.7	0.80	44.861*** (I>II,IV)#	-9.040***
6 months[f]										10.6	4.4	0.77	35.018*** (I>II,IV)#	-7.839***
18 months										11.2	4.5	0.78	24.209*** (I>II,IV)#	-6.262***
At index interview[h]										11.3	4.5		22.644*** (I>II,IV)#	-5.482***

[a] ANOVA was computed between groups I, II and IV at baseline and using baseline data from groups I and II as a reference for group IV at 6 months and 18 months

[b] t-test was computed between groups III and IV at baseline and using baseline data from group I as a reference for group IV at 6 months and 18 months

[c] missing data 4/338, 1/50, 5/388

[d] missing data 3/338, 1/50, 4/388

[e] missing data 4/338, 4/193, 4/388

[f] missing data 2/193

[g] missing data 5/338, 5/388, 4/193

[h] Interview, when scores on the Hamilton Depression Scale were at a minimum

*** $p<0.001$

[#] Significant differences based on post-hoc (Tukey) group comparisons

7.3.2.3 Correlations between neuroticism and extraversion and test-retest correlations

N scores correlated negatively with those on the E scale at different time points (baseline: r=-0.242, p<0.01; 6-month follow-up: r=-0.438, p<0.001; 18-month follow-up: r=-0.426, p<0.001).The test-retest correlation for N increased during the follow-up (baseline and 6-month follow-up: r=0.496, p<0.001; baseline and 18-month follow-up: r=0.486, p<0.001; 6-month and 18-month follow-up: r=0.737, p<0.001), and for E decreased slightly (baseline and 6-month follow-up: r=0.753, p<0.001; baseline and 18-month follow-up: r=0.688, p<0.001; 6-month and 18-month follow-up: r=0.731, p<0.001).

7.3.2.4 Multivariate models for the 'state effect'

In multiple regression models (Table 12.) with 18-month follow-up N or E scores as dependent variables, and age, gender, marital status, education, work status, change in BDI and BAI scores between two time points (18-month follow-up and baseline), and either baseline N or E as independent variables, 18-month follow-up N was significantly explained by baseline N, education and change in both BDI and BAI scores and 18-month follow-up E was explained by baseline E, age and change in BDI scores. Due to correlations between the scores of BDI, BAI, N and E, the analyses were performed also by using HAM-D instead of BDI, but the results remained the same.

Table 12. Multiple regression models for the 'state effect'. [a]

Dependent variable								
	Neuroticism[b]				Extraversion[c]			
Independent variable	β-coefficient[*]	t	p	Partial R^2	β-coefficient[*]	t	p	Partial R^2
Neuroticism, baseline	0.520	9.482	<0.001	0.267				
Extraversion, baseline					0.656	12.333	<0.001	0.400
BDI, change 18 months and baseline	0.278	4.401	<0.001	0.058	-0.166	-2.800	0.006	0.020
BAI, change 18 months and baseline	0.201	3.261	0.001	0.032	-0.029	-0.501	0.617	0.001

[*] Standardized coefficient
[a] Also adjusted for age, gender, education, marital status and work status
[b] 18-month follow-up neuroticism, R^2=0.456,F(8,175)=20.176,p<0.001
[c] 18-month follow-up extraversion, R^2=0.523,F(8,175)=26.066,p<0.001

BDI=Beck Depression Inventory, BAI=Beck Anxiety Inventory

7.3.3 Comparisons for the 'scar effect'

The number of preceding lifetime depressive episodes correlated mildly with both the N scores (r_s=0.28, p<0.001) and E (r_s=-0.16, p=0.031). Altogether 94 patients (67 females and 27 males) had a recurrence or a relapse (mean duration 4.6 months, sd 4.3 months) between the 6- and 18-month follow-ups. However, during this time, there were no significant differences in N (16.5, sd 4.3 vs. 16.2, sd 4.8, p=ns) or E (9.6, sd 4.5 vs. 10.2, sd 4.6, p=ns) scores. The results remained the same even when the subgroups by the lifetime number of depressive episodes (lifetime second 26% [N=24], third 33% [N=31], fourth 15% [15] and fifth or more 26% [N=24]) were analyzed separately. No gender differences were found.

7.3.4 Comparisons for the 'trait effect'

7.3.4.1 Neuroticism and extraversion, age and gender

Both female and male patients from the VDS scored significantly higher on the N scale and lower on the E scale than subjects from the general population. Age correlated negatively, with no gender differences, with the index interview E scores from the VDS cohort (r=-0.284, p<0.001) as well as with the scores from the general population (r=-0.226, p<0.001), but not significantly with the N scores from either group.

7.3.4.2 Neuroticism and extraversion scales and BDI and BAI scores

BDI and BAI scores correlated strongly with N scores of MDD patients at the index interview (r_s=0.626, p<0.001 and r_s=0.721, p<0.001, respectively) and moderately with E scores (r_s=-0.425, p<0.001 and r_s=-0.378, p<0.001). Likewise, in the general population, the BDI and the BAI scores correlated strongly with N (r_s=0.712, p<0.001 and r_s=0.689, p<0.001, respectively) and moderately with E (r_s=-0.479, p<0.001 and r_s=-0.373, p<0.001). In MDD patients at the index interview and in the general population, the correlation between BDI and BAI was strong (r_s=0.672, p<0.001 and r_s=0.731, p<0.001, respectively). No significant gender differences in these correlations were found.

7.3.4.3 Logistic regression models for the 'trait effect'

In a logistic regression model after controlling for gender, marital status, work status, education, age and BDI and BAI scores, being a depressive patient was associated with higher N (OR 1.11, p=0.001) and lower E (OR 0.92, p=0.003) scores.

7.4 Neuroticism, extraversion and comorbidity of MDD

7.4.1 Comorbid axis I disorders

As the level of N increased, the prevalences of any comorbid axis I disorder and anxiety disorder, especially phobic and alcohol dependence increased, whereas as the level of E decreased the prevalence of comorbid social phobia increased. The prevalences of different comorbid disorders by level of N and E are shown in Table 13.

In a logistic regression model, after controlling for HAM-D, gender and age, having any comorbid axis I or anxiety disorder, especially phobic disorder, was associated with higher N (OR 1.08, p=0.027; OR 1.07; p=0.043; OR 1.11 p=0.002, respectively), while having comorbid social phobia was associated with lower E (OR 0.87, p=0.007).

7.4.2 Comorbid axis II disorders

As the level of N increased, the prevalence of any comorbid axis II disorder, cluster C personality disorder, especially avoidant personality disorder, and borderline personality disorder increased, whereas as the level of E decreased the prevalence of any comorbid axis II disorder, cluster C personality disorder, especially avoidant, and, as a trend, cluster A personality disorder (p=0.07) increased. The prevalences of different comorbid axis II disorders by level of N and E are shown in Table 13.

In a logistic regression model, after controlling for HAM-D, gender and age, having any comorbid axis II disorder, cluster C personality disorder or avoidant personality disorder, was associated with high N (OR 1.15, p=0.007; OR 1.32, p<0.001; OR 1.27, p=0.002, respectively), whereas having comorbid cluster A, paranoid, cluster C or avoidant personality disorder was associated with lower E (OR 0.84, p=0.015; OR 0.82, p=0.01; OR 0.82, p=0.001; OR 0.76, p<0.001, respectively).

In the multiple linear regression model, with the number of positive items of different comorbid axis II disorders as a dependent variable and HAM-D, gender, and age either N or E as independent variables comorbid paranoid (β=0.077, sd 0.021, p<0.001), borderline (β=0.127, sd 0.024, p<0.001) and all cluster C personality disorders: avoidant (β=0.109, sd 0.025, p<0.001), dependent (β=0.075, sd 0.019, p<0.001), obsessive-compulsive (β=0.084, sd 0.021, p<0.001), passive-aggressive (β=0.070, sd 0.023, p<0.01) were significantly explained by N, whereas comorbid paranoid (β=-0.059, sd 0.025, p<0.05), schizoid (β=-0.042, sd0.017, p<0.05) and avoidant (β=-0.192, sd 0.028, p<0.001) personality disorders were explained by E.

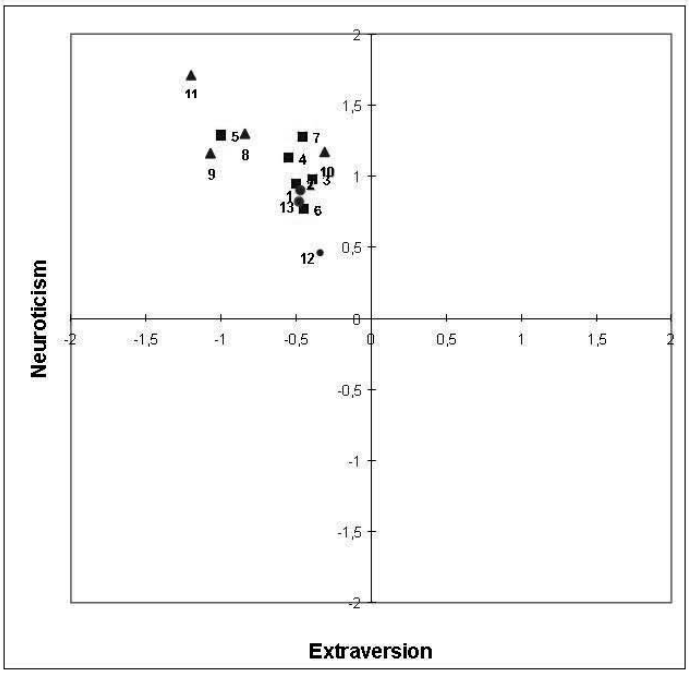
7.4.3 Number of comorbid disorders

As the level of N increased, the mean number of comorbid axis I, II or both axes disorders increased, whereas as the level of E decreased the number of comorbid axis II disorders increased (Table 13).

In the multiple linear regression model (Table 14), with the number of comorbid disorders (either axis I or II or both axes I and II) as a dependent variable and HAM-D, gender, age, and either N or E as independent variables, the number of comorbid disorders in all three models was significantly explained by N, but not by E.

7.4.4 Comparison between axis I and II comorbid disorders

Among patients with pure MDD or with any comorbid axis I or II disorder, the standardized scores of N were +0.46, +0.90 and +1.30, respectively, and the scores of E -0.34, -0.47 and -0.84, respectively. The comorbid disorder specific standardized scores of N and E are shown in Figure 1.



1= Any axis I disorder
2= Any anxiety disorder
3= Panic Disoder
4= Phobic disorder
5= Obsessive-Compulsive Disorder
6= Generalised Anxiety Disorder
7= Alcohol dependence
8= Any personality disorder
9= Cluster A personality disorder
10= Cluster B personality disorder
11= Cluster C personality disorder
12= Pure MDD
13= All patients

Figure 1. Mean neuroticism (N) and extraversion (E) scores of axis I and II comorbid disorders of Major Depressive Disorder (MDD) patients (N=193) in the Vantaa Depression Study converted into standardized scores.
(origo: mean scores of N and E in the general population).

Table 13. Prevalence (number of patients) having comorbid axis I or II disorder, atypical or melancholic depression, mean number (range) of comorbid disorders, and mean scores of Social and Occupational Functioning Assessment Scale of DSM-IV (SOFAS) by four levels of neuroticism (based on population mean and standard deviation) in Vantaa Depression Study (N=193).

	Neuroticism score[a,b]					
Characteristic	Low < -1 sd (I)(14)	Normal -1 sd - +1 sd (II)(81)	High +1 sd - +2 sd (III)(66)	Very high >+2 sd (IV)(30)	χ^2	p
No comorbid disorder	14.3 (2)	21.0 (17)	4.5 (3)	0 (0)	14.335[d]	0.001
Axis I diagnosis[h]						
Any axis I disorder	57.1 (8)	58.0 (47)	80.3 (53)	73.3 (22)	9.455[c]	0.024
Any anxiety disorder	57.1 (8)	55.6 (45)	77.3 (51)	70.0 (21)	8.288[c]	0.040
Panic disorder	21.4 (3)	13.6 (11)	28.8 (19)	20.0 (6)		ns
Any phobic disorder[f]	28.6 (4)	37.0 (30)	59.1 (39)	63.3 (19)	12.091[c]	0.007
Agoraphobia without panic	0 (0)	9.9 (8)	18.2 (12)	26.7 (8)	7.532[f]	0.049
Social phobia	14.3 (2)	14.8 (12)	30.3 (20)	33.3 (10)		ns
Simple phobia	21.4 (3)	28.4 (23)	48.5 (32)	46.7 (14)	8.860[c]	0.031
Obsessive-compulsive disorder	0 (0)	4.9 (4)	15.2 (10)	10.0 (3)		ns
Generalized anxiety disorder	14.3 (2)	13.6 (11)	16.7 (11)	13.3 (4)		ns
Alcohol dependence	14.3 (2)	7.4 (6)	16.7 (11)	36.7 (11)	14.236[c]	0.003
Axis II diagnosis[b,g]						
Any personality disorder	0 (0)	16.0 (13)	42.4 (28)	43.3 (13)	22.218[d]	<0.001
Cluster A	0 (0)	6.2 (5)	12.1 (8)	13.3 (4)		ns
Paranoid	0 (0)	4.9 (4)	10.6 (7)	13.3 (4)		ns
Cluster B	0 (0)	8.6 (7)	21.2 (14)	16.7 (5)		ns
Borderline	0 (0)	2.5 (2)	13.6 (9)	16.7 (5)	9.683[d]	0.013
Cluster C	0 (0)	2.5 (2)	28.8 (19)	43.3 (13)	36.474[d]	<0.001
Avoidant	0 (0)	1.2 (1)	21.2 (14)	33.3 (10)	27.771[d]	<0.001
Number of comorbid disorders						
Axis I disorder, mean (sd)	0.86(0.94)	0.93(1.03)	1.74(1.21)	1.87(1.70)	21.211[c,e]	<0.001
Axis II disorder, mean (sd)	0 (0)	0.20(0.51)	0.74(1.09)	0.83(1.05)	24.714[c,e]	<0.001
Axis I and II disorder, mean (sd)	1.00(0.96)	1.22(1.19)	2.63(1.87)	2.80(2.06)	34.614[c,e]	<0.001
Subtypes of depression						
Atypical depression	7.1 (1)	11.1 (9)	21.2 (14)	23.3 (7)		ns
Melancholic features	35.7 (5)	35.8 (29)	47.0 (31)	50.0 (15)		ns
Level of functioning[b]						
SOFAS score, mean (sd)[l]	82.1 (10.7)	79.1 (11.0)	67.5(14.5)	67.7 (12.6)	I,II>III,IV[j]	<0.001

[a] Missing data: 2/193
[b] At index interview, when scores on the Hamilton depression Scale were at a minimum.
[c] df=3
[d] Fisher's exact test
[e] Kruskall-Wallis test
[f] Agoraphobia without panic + social phobia + simple phobia
[g] Separate personality disorders were included, if n>10
[h] At any time (baseline, 6 months or 18 months)
[j] ANOVA, F=14.712, df=3, post-hoc (Tukey)
[k] ANOVA, F= 6.461, df=3, post-hoc (Tukey)
[l] Missing data 3/193

Extraversion score[a,b]						
Very low < -2 sd (I)(10)	Low -2 sd - -1 sd (II)(61)	Normal -1 sd - +1 sd (III)(108)	High >+1 sd (IV)(12)	χ^2	p	Characteristic
0 (0)	8.2 (5)	14.8 (16)	8.3 (1)		ns	No comorbid disorder
						Axis I diagnosis[h]
80.0 (8)	70.5 (43)	64.8 (70)	75.0 (9)		ns	Any axis I disorder
70.0 (7)	68.9 (42)	63.0 (68)	66.7 (8)		ns	Any anxiety disorder
10.0 (1)	19.7 (12)	21.3 (23)	25.0 (3)		ns	Panic disorder
60.0 (6)	54.1 (33)	44.4 (48)	41.7 (5)		ns	Any phobic disorder[f]
30.0 (3)	21.3 (13)	9.3 (10)	16.7 (2)		ns	Agoraphobia without panic
50.0 (5)	32.8 (20)	16.7 (18)	8.3 (1)	11.306[c]	0.010	Social phobia
50.0 (5)	39.3 (24)	36.1 (39)	33.3 (4)		ns	Simple phobia
10.0 (1)	16.4 (10)	5.6 (6)	0 (0)		ns	Obsessive-compulsive disorder
20.0 (2)	16.4 (10)	13.9 (15)	8.3 (1)		ns	Generalized anxiety disorder
10.0 (1)	16.4 (10)	16.7 (18)	8.3 (1)		ns	Alcohol dependence
						Axis II diagnosis[b,g]
70.0 (7)	39.3 (24)	19.4 (21)	16.7 (2)	17.221[c]	0.001	Any personality disorder
30.0 (3)	9.8 (6)	7.4 (8)	0 (0)		ns(0.07)	Cluster A
20.0 (2)	9.8 (6)	6.5 (7)	0 (0)		ns	Paranoid
10.0 (1)	11.5 (7)	14.8 (16)	16.7 (2)		ns	Cluster B
0 (0)	11.5 (7)	6.5 (7)	16.7 (2)		ns	Borderline
60.0 (6)	31.1 (19)	8.3 (9)	0 (0)	25.727[d]	<0.001	Cluster C
50.0 (5)	26.2 (16)	3.7 (4)	0 (0)	28.067[d]	<0.001	Avoidant
						Number of comorbid disorders
1.80(1.69)	1.62(1.50)	1.19(1.11)	1.00(0.85)		ns	Axis I disorder, mean (sd)
1.10(0.99)	0.59(0.82)	0.36(0.88)	0.33(0.89)	16.198[c,e]	0.001	Axis II disorder, mean (sd)
3.10(2.28)	2.28(1.87)	1.70(1.62)	1.42(1.24)		ns	Axis I and II disorder, mean (sd)
						Subtypes of depression
30.0 (3)	14.8 (9)	16.7 (18)	8.3 (1)		ns	Atypical depression
50.0 (5)	45.9 (28)	38.0 (41)	50.0 (6)		ns	Melancholic features
						Level of functioning[b]
63.6 (14.3)	69.7 (13.9)	75.6 (13.0)	82.8 (10.9)	I,II<III,IV[k]	<0.001	SOFAS score, mean (sd)[l]

Table 14. Multivariate analysis[a] with the number of comorbid disorders (all axis I or any anxiety or all axis II or both axis I and II) as a dependent variable and either neuroticism (N) or extraversion (E) separately or together as an independent variable in depressive patients (N=193).

Independent variable	Anxiety disorders[b]			All axis I disorders[b,c]			Personality disorders[d]			Axis I[b,c]+II disorder[d]		
Entered separately	β	t	p	β	t	p	β	t	p	β	t	p
1) N[e]	0.239	2.903	0.004	0.264	3.254	0.001	0.228	2.780	0.006	0.311	3.965	<0.001
2) E[e]	-0.123	-1.529	ns	-0.085	-1.065	ns	-0.128	-1.596	ns	-0.128	-1.639	ns
Entered together												
3) N[e]	0.220	2.578	0.011	0.258	3.066	0.002	0.207	2.434	0.016	0.297	3.639	<0.001
4) E[e]	-0.066	-0.804	ns	-0.018	-0.226	ns	-0.074	-0.905	ns	-0.051	-0.654	ns

[a] Linear regression models, adjusted for the Hamilton Depression Scale scores, age and gender
[b] At any time (baseline, 6 months or 18 months)
[c] Anxiety disorders + alcohol dependence
[d] At index interview, when scores on the Hamilton Depression Scale were at a minimum
[e] Missing data 2/193

8. DISCUSSION

8.1 Main findings

The revised version of the temperament and character inventory (TCI-R) has been seldom applied to investigate anxiety among subjects in the general population and this was one of the first of such studies. Both the temperament dimension of Harm Avoidance and character dimension of Self-Directedness were found to associate significantly with symptoms of anxiety as well as depression. Self-reported positive family history of mental disorders associated somewhat with Harm Avoidance, but not with Self-Directedness. Moreover, both the dimensions were also weakly associated with health care use and self-reported mental disorders.

There are also only few previous studies on the relationships between neuroticism and extraversion and the symptoms of anxiety and depression in the general population. Both the personality dimensions of extraversion and neuroticism were found to be strongly associated with depression and anxiety. Lifetime mental disorder and self-reported health care use for psychiatric reasons were also associated with neuroticism, the former as strongly as BAI and BDI scores.

Among major depressive disorder patients, the scores of neuroticism were observed to decline markedly and the scores of extraversion to increase somewhat with recovery. The predictive value of the changes in symptoms of anxiety and depression in explaining follow-up neuroticism was about 1/3 of that of baseline neuroticism. In contrast to neuroticism, extraversion scores showed no dependence on the symptoms of anxiety, and the change in the symptoms of depression explained only 1/20 of the follow-up extraversion compared with baseline extraversion. During a 12-month follow-up period, no evidence of the 'scar effect' was found. MDD patients had a markedly higher level of neuroticism and a slightly lower level of extraversion than subjects in the general population, even after controlling for symptoms of both anxiety and depression,

In MDD patients a positive dose-exposure relationship was found between the level of neuroticism and the number and prevalence of comorbid axis I and II disorders. Likewise, a negative dose-exposure relationship was consistently observed between the level of extraversion and social phobia and cluster C personality disorders, and less consistently with cluster A personality disorders. All patients with or without comorbid disorder had positive standardized scores of neuroticism and negative of extraversion, but the scores were not grossly extreme in any patient group.

8.2 Strengths and limitations of the study

8.2.1 General population survey

8.2.1.1 Representativeness of the sample

The sample was randomly drawn from the National Population Register, representing the adult population of two larger Finnish cities. The response rate for the whole questionnaire was rather low (38.6%) and the sample size remained moderate (N=347), possibly due to the length of the questionnaire (30-60 minutes to complete). However, the response rate rose somewhat (49%) and sample size increased (N=441) when the responders of the shortened version of the questionnaire were also included. There were only minimal differences in sociodemographic characteristics between responders and the general population. The responders were somewhat older, a little better educated, slightly more often married and employed. It is not known whether the results are generalizable to rural populations, as the sample included only suburban and urban population.

8.2.1.2 Temperament and personality dimensions measured

Although no marked differences in the characteristics between responders and non-responders emerged, and the mean scores of TCI-R and EPI among the responders were comparable to the other general population studies using the TCI-R (Brandstrom et al. 2003; Gutierrez-Zotes et al. 2004) and EPI, (Eysenck and Eysenck 1964), the possibility that the population could have been biased towards some temperament or character dimension investigated (e.g. P or ST) cannot be excluded. Moreover, even though the distributions of anxiety and depressive symptoms scores were as expected, the question of how much current mood state affected the scores of either temperament and character dimensions or extraversion and neuroticism remains open, due to the study's cross-sectional design. However, the internal consistency of the Finnish version of the TCI-R was good (Cronbach's alpha from 0.85 to 0.89), as well as that of the Finnish version of the N and E scales (Cronbach's alpha 0.85 and 0.79).

8.2.2 MDD patient cohort

8.2.2.1 Representativeness of the sample

The VDS comprised a cohort of 269 in- and outpatients with MDD, effectively representing all psychiatric patients with a new episode of MDD in the Finnish city of Vantaa. Two thirds of all depressed subjects in the general population of Vantaa seeking treatment from psychiatrists are treated in the PMCD (Rytsälä et al. 2001). This study took place during the era of modern antidepressants in 1997-1999 in a community psychiatric setting; at baseline 78% of the patients received antidepressants at adequate levels during the acute phase in compliance with the APA Practice Guideline (Melartin et al. 2004).

8.2.2.2 Diagnostic measures

The patients of the study were diagnosed carefully using semi-structured interviews with excellent reliability (kappa=0.86) for the diagnosis of MDD. However, the reliability of comorbid disorder diagnosis remains unknown. Axis II diagnoses were assessed using the semi-structured SCID-II interview for DSM-III-R, as the SCID-II for DSM-IV was not yet available in February 1997. The differences between DSM-III-R and DSM-IV were taken into account by excluding masochistic personality disorder. Passive-aggressive personality disorder was included because it belongs to the "personality disorder not otherwise specified" category in DSM-IV

8.2.2.3 Life-chart methodology

The Longitudinal Interval Follow-up Evaluation (LIFE) methodology was introduced in the NIMH-CDS to investigate the outcome of depression (Keller et al. 1987). In the VDS the course of depression was assessed during the follow-up by using a graphic life-chart methodology similar to, but not identical to LIFE. All patient records and monthly BDI-ratings (for the first 6 months) were available. Patients' follow-up time was classified into periods of DSM-IV MDE, partial or full remission.

8.2.2.4 Drop outs

Altogether 73% of the cases could be interviewed at all three time points and their depression had remained unipolar (the diagnosis switched to bipolar in 13/269 patients, 5%). As the factors associated with dropping out were younger age and a slightly higher score on the baseline BAI scale, but not differences in other sociodemographic variables or in BDI, N or E, the percentage of drop outs is unlikely to have biased the findings.

8.2.2.5 Comorbid axis I and II disorders

Only current axis I diagnoses assigned at the three follow-up time points were included. Thus, the prevalence of these comorbid disorders might have been underestimated during the follow-up. All comorbid axis II disorders could not be analysed separately, and also it is possible that all differences within axis I comorbidity could not be detected, both due to the small number of cases in the subgroups.

8.2.2.6 Personality dimensions measured

The personality dimensions were measured only by EPI, as at baseline, the Finnish version of TCI-R was not yet available. The internal consistency of EPI was good (Cronbach's alphas for N and E at baseline, 6 months and 18 months were 0.73, 0.85, 0.87 and 0.80, 0.77, 0.78, respectively). As there were no premorbid measurements of personality dimensions in MDD patients, it is not possible to completely rule out the possibility that the differences in the level of N and E found between MDD patients and the general

population might have partly been a consequence of a post-morbid change of personality in MDD patients. However, the majority of the MDD patients were in their lifetime first, second or third episode at baseline, there was no evidence for a change on the N or E scores in any of these subgroups after subsequent relapses or recurrences of MDD, and E and N scores when HAM-D scores were at minimum were used. Thus, if post-morbid changes would have explained the differences between the patients and the general population, then they must have had developed immediately during the lifetime first episode. However, this possibility is unlikely.

8.3 Temperament and personality dimensions and the dimensional concept of anxiety and depression

In the present study, the personality dimensions associated not only to the symptoms of depression, but also to the symptoms of anxiety among the general population and in depressive patients, as well as to comorbid disorders in MDD patients, supporting the dimensional view of depression and anxiety (Helzer et al. 2006). The relationship between the symptoms of anxiety and depression and the personality dimensions of neuroticism and of extraversion, as well as the temperament and character dimensions of TCI-R, was studied among the general population. There are only few previous general population studies (Goodwin et al. 2002; Bienvenu et al. 2004; Cox et al. 2004) investigating the association between the dimensions of N and E and anxiety and depressive symptoms, and none has explored anxiety symptoms with both dimensions. Moreover, there are even less studies (Grucza et al. 2003; Richter et al. 2003) investigating the relationship between the dimensions of TCI-R and the symptoms of depression undertaken in the general population, and none on anxiety.

The association between MDD and neuroticism and extraversion was investigated longitudinally among a cohort of depressive patients. By having the N and E scores of the general population, it was possible to study these two dimensions not only among the MDD patients at different time points, but also to compare the level of N and E between the general population and MDD patients. The relationship between N and E and MDD has been studied in some prospective epidemiological twin (Kendler et al. 1993b, 2006a; Fanous et al. 2007) and general population studies (Ormel et al. 2004). However, it is uncertain whether the findings of an epidemiological study are generalizable to clinical samples, as patients from clinical samples commonly tend to have longer-lasting, more severe and recurrent episodes, often comorbid with personality disorders. There are some previous longitudinal premorbidly started clinical studies among primiparous women (Boyce et al. 1991), family members of patients with depression (Hirschfeld et al. 1989; Shea et al. 1996) or male conscripts (Angst and Clayton 1986) investigating the association between MDD and the dimensions of N and E, but as a limitation of these studies, the state of anxiety, which also might influence on the scores of N and E (Reich et al. 1986), was not controlled and the sample was restricted to a limited patient group.

As all comorbid disorders were assessed in MDD patients, it was possible to study the relationship between N and E and MDD with both axis I and II comorbid disorders to obtain an overall picture of these associations. Former studies have explored either axis I (Bienvenu et al. 2001; Khan et al. 2005; Hettema et al. 2006) or all (Davidson et al. 1985; Brieger et al. 2000) or only one (Khan et al. 2005) axis II comorbid disorders, but not both axes concurrently. Moreover, only one previous study of MDD and comorbid disorders, evaluating MDD and comorbid GAD, has been longitudinal and controlled for the possible confounding state-effect of depression.

8.4 Temperament and personality dimensions and the symptoms of depression

Among the general population neuroticism and Harm Avoidance, both measuring sensitivity to negative stimuli, were found to associate positively with the symptoms of depression measured by BDI. These findings are consistent with earlier reports with HA and depressive symptoms in clinical settings (Svrakic et al. 1992; Joffe et al. 1993; Hansenne et al. 1999), among students (Peirson and Heuchert 2001) and in the general population (Richter et al. 2003), as well as with N and depressive symptoms in clinical (Kendell and DiScipio 1968; Ulusahin and Ulug 1997) and non-clinical (Hepburn and Eysenck 1989; Williams 1990; Saklofske et al. 1995) settings, in patients and their healthy controls (Hirschfeld et al. 1983a; Farmer et al. 2002) and among the general population (Bienvenu et al. 2004).

By contrast, extraversion, a trait reflecting a tendency to experience positive mood states and the character dimension of Self-Directedness, based on a concept of the self as an autonomous individual, associated negatively with depressive symptoms measured by BDI among the general population. These results accord with previous findings with E and depressive symptoms in clinical (Kendell and DiScipio 1968; Ulusahin and Ulug 1997) and non-clinical (Hepburn and Eysenck 1989; Williams 1990; Saklofske et al. 1995) settings, in patients and their healthy controls (Hirschfeld et al. 1983a; Farmer et al. 2002) and among the general population (Bienvenu et al. 2004), as well as with SD and depressive symptoms in clinical settings (Svrakic et al. 1992; Joffe et al. 1993; Hansenne et al. 1999), among students (Peirson and Heuchert 2001) and in the general population (Richter et al. 2003). All the association remained significant even after adjusting for education, gender and age.

8.5 Temperament and personality dimensions and the symptoms of anxiety

Both high N and high HA associated with the symptoms of anxiety, measured by BAI, even after adjustment for gender, education and age. This finding is consistent with previous reports with N and anxiety symptoms conducted in twins (Hettema et al. 2004), in clinical settings (Kerr et al. 1970; Bianchi and Fergusson 1977), in students (Bull and Strongman 1971; De and Singh 1972) and in the general population (Henderson et al. 1998; Issakidis and Andrews 2002). Also in earlier clinical studies (Pfohl et al. 1990; Ball et al. 2002; Marteinsdottir et al. 2003) and studies among students (Pelissolo et al. 2002; Jiang et al. 2003) a positive association between HA and anxiety has been observed. Moreover, although P did not associate positively with the symptoms of anxiety in the univariate analyses, in the multiple regression models the temperament dimension of P and the character dimension of ST associated positively with the symptoms of anxiety.This finding, however, may be due to multicollinearity problems.

Symptoms of anxiety correlated negatively with both E and SD. The negative association between SD and the symptoms of anxiety was confirmed in the multiple regression models, even after adjustment for gender, education and age. This finding accords with former studies conducted among students (Pelissolo et al. 2002; Jiang et al. 2003) and in clinical settings (Pfohl et al. 1990; Ball et al. 2002; Marteinsdottir et al. 2003). Although E correlated negatively with anxiety symptoms, the association was not confirmed in the multiple regression models, perhaps due to the negative correlation between N and E scores. However, this negative finding accords fully with the view that E is related to depression only, but not with anxiety (Clark et al. 1994).

8.6 Temperament and personality dimensions and health related questions

The overall clinical significance of the associations between the symptoms of depression and anxiety and the temperament and personality dimensions measured among the general population was supported by the data obtained from the health related questions. The BDI and BAI scores, as well as HA and N scores correlated positively, while P negatively with the questions on health care use for mental health problems during the past year, self-reported mental health disorder in relatives and self-reported but physician-diagnosed lifetime mental disorder. SD and E correlated negatively with self-reported lifetime mental disorder and self-reported health care use for a mental health problem during the past year. HA, but not other dimensions correlated somewhat with self-reported positive family history of mental disorders. These preliminary findings need to be interpreted with caution, as their validity, particularly the self-reported family

history, is unknown. However, the prevalence of self-reported health care use in the present study fully accords with their known prevalence in the Finnish general population (Hämäläinen et al. 2004), and high N and HA were found to associate nearly as strongly as the symptoms of anxiety and depression with the self-reported health care use. Moreover, in previous studies the use of mental health services for anxiety disorders (Issakidis and Andrews 2002) has been found to associate with high N, or for anxiety and depressive disorders (Goodwin et al. 2002) with high N and low E.

8.7 Personality dimensions and MDD

8.7.1 Neuroticism

High N associated with the symptoms of depression and anxiety in MDD patients. Moreover, N was found to be dependent on the change in symptoms of both depression and anxiety. As the dispersion of the depressive symptoms increased during the follow-up, the correlations between N and the symptoms of depression and anxiety expectedly strengthened among the MDD patients, reaching nearly the level of the general population. The dependence on the change in symptoms of depression is consistent with earlier clinical studies (Kendell and DiScipio 1968; Hirschfeld et al. 1983b). However, only a few earlier studies (Bianchi and Fergusson 1977; Clark et al. 1994) have reported the dependence of N on the change in symptoms of anxiety. In accordance with a previous five-week study (Santor et al. 1997) the follow-up N scores were only marginally accounted for, by the changes in depression scores and mostly by the baseline personality dimensions. The changes in symptom state explained only 1/3 (depression 2/9 and anxiety 1/9) of what the baseline N explained of the follow-up N. Thus, although being relatively stable, N was found to be also state-dependent on both depressive and anxiety symptoms.

During the 12-month follow-up, the N scores did not change in a subgroup of MDD patients with a recurrence or relapse of depression, which is consistent with a 18-year follow-up study (Duggan et al. 1991) and also with premorbidly started studies (Shea et al. 1996; Ormel et al. 2004). However, this finding is contrary to some epidemiological studies (Kendler et al. 1993b), where the level of N was increased possibly due to residual mild symptoms of depression. Thus, in the present study N was not found to be shaped by a relapse or recurrence of depression.

Even after controlling for symptoms of anxiety and depression and other confounding sociodemographic factors, the scores of N were higher among MDD patients than in the general population. This finding accords with previous reports (Hirschfeld and Klerman 1979; Angst and Clayton 1986; Ormel et al. 2004; Kendler et al. 2006a). The difference in the proportion of subjects in the depressive group with very high N, i.e. over 2 sd above the mean N score of the general population was 7-fold (18% vs. 2.5%) that of the general population, which is in line with an earlier study with depressive patients and published norms (Hirschfeld and Klerman 1979) and with a prospective general population group (Ormel

et al. 2004). However, less than 20% of depressive patients had extreme N scores, and the range of scores among depressive patients and the general population had a large overlap. Overall, these findings were consistent with the view that N is a risk factor or at least indicator for MDD.

8.7.2 Extraversion

The personality dimension of extraversion was found to be dependent on the change in symptoms of depression and anxiety. During the follow-up the correlations between E and the symptoms of depression and anxiety strengthened among the MDD patients, reaching nearly the level of the general population. The dependence on the change in symptoms of depression is consistent with most earlier clinical (Kendell and DiScipio 1968; Hirschfeld et al. 1983b), but not all epidemiological (Kendler et al. 1993b) studies. In accordance with a previous five-week study (Santor et al. 1997) the follow-up E scores were mostly accounted for by the baseline E scores, and only marginally by the changes in depression scores. The changes in symptom state explained only 1/20 of what the baseline E explained of the follow-up E. Overall, although relatively stable, E showed to be state-dependent on depressive symptoms, but not on anxiety symptoms.

The scores of E did not change during the 12-month period in a subgroup of MDD patients with a recurrence or relapse of depression, which is consistent with a previous premorbidly started study (Shea et al. 1996). Overall, E was not found to be shaped by a relapse or recurrence of depression.

Even after controlling for symptoms of anxiety and depression and other confounding sociodemographic factors, the scores of E were lower among MDD patients than in the general population. This is consistent with some previous clinical (Hirschfeld et al. 1983a; Farmer et al. 2002) and general population twin studies (Kendler et al. 2006a), but not all (Kendler et al. 1993b), where E and major depression had no significant relationship. The difference in the percentage of subjects with very low E, i.e. less than 2 sd below the mean E score of the general population was 4-fold (10% vs. 2.5%) among depressive patients compared with the general population, slightly less than in another study with depressive inpatients and published norms (18% vs. 2.5%) (Hirschfeld and Klerman 1979). Although the difference in the level of E between MDD patients and the general population was not as pronounced as with N, it was clearly observed. The lower level of E seen in clinical rather than in general population studies (Kendler et al. 1993b) of depression might at least be in part due to the high rate of comorbidity of depression and personality disorders, especially cluster C (32 %, Melartin et al. 2002) among MDD patients. Albeit not as strong as N, low E i.e. introversion, was found to be a risk factor or indicator for MDD.

8.8 Personality dimensions and MDD with comorbid axis I or II disorders

8.8.1 MDD with comorbid axis I disorders

High N was found to associate with comorbid axis I disorders. Moreover, a positive dose-exposure relationship was found between the level of N and the number and prevalence of comorbid axis I disorders. Only phobic disorders associated with high N, consistent with previous reports (Bienvenu et al. 2001; Khan et al. 2005; Weinstock and Whisman 2006), whereas other internalizing (panic disorder, GAD) and externalizing disorders did not reach statistical significance, perhaps due to too few cases. The positive association between N and the number of comorbid axis I disorders has also been noted in earlier studies (Bienvenu et al. 2001; Cuijpers et al. 2005). Even after adjustment for gender, age and HAM-D scores, all the above associations remained significant.

Of comorbid axis I disorders, low E associated with social phobia. In accordance with an earlier study (Bienvenu et al. 2001), a negative dose-response relationship was observed between the level of E and the prevalence of social phobia. However, contrary to a previous report investigating MDD and comorbid anxiety disorders, using NEO Five-Factor Inventory and not controlling for the current symptoms of depression (Cuijpers et al. 2005), the number of comorbid axis I disorders was not dependent on the level of E. Even after adjustment for gender, age and HAM-D scores, all associations remained significant. Thus, the role of E in comorbidity seems to be more specific than that of N.

8.8.2 MDD with comorbid axis II disorders

High N associated with cluster C personality disorders, especially with avoidant personality disorder. Moreover, a clear positive dose-exposure relationship was found between the level of N and number and prevalence of comorbid axis II disorders. When applying the number of positive personality disorder items, a positive correlation was also found between the N scores and paranoid, borderline and all cluster C (avoidant, dependent, obsessive-compulsive, passive-aggressive) personality disorders, which accords with a previous finding (Brieger et al. 2000). As a new finding, high N was found to associate also with the number of comorbid axis II disorders. All associations remained significant even after adjustment for gender, age and HAM-D scores. Overall, among MDD patients, high N was found to predict comorbidity of axis II disorders, as well as the overall number of comorbid axis II disorders.

A negative dose-response relationship was observed between the level of E and the prevalence of cluster C and also, as a trend, cluster A personality disorder. In accordance with a previous report (Brieger et al. 2003), low E associated with avoidant and paranoid personality disorders and, when applying the number of positive personality disorder items, also with schizoid personality disorder. Even after adjustment for gender, age and HAM-D scores, all the associations remained significant. The role of E in axis II comorbidity seems to be more specific than that of N.

8.8.3 Personality dimensions and pure MDD or with any comorbid axis I or II disorders

The scores of N and E were not extreme for patients with either pure MDD or with comorbid axis I or II disorders, although their overall psychopathology increased as the N scores increased, and, but to a lesser extent, as the E scores decreased. Moreover, for all of these patient groups the pattern of these scores was the same. The standard scores of N were positive and those of E negative, which accords with the view that high N broadly and low E weakly are common vulnerability factors for comorbid psychiatric disorders of MDD (Khan et al. 2005).

9. CONCLUSIONS AND FUTURE IMPLICATIONS

9.1. Conclusions and clinical implications

Personality dimensions associated not only to the symptoms of depression, but also to the symptoms of anxiety among general population and in depressive patients, as well as to comorbid disorders in MDD patients, supporting the dimensional view of depression and anxiety. Among subjects in the general population, the temperament dimension Harm Avoidance and the character dimension Self-Directedness associated moderately, whereas extraversion and neuroticism strongly with the depressive and anxiety symptoms. The temperament and personality dimensions, especially Harm Avoidance, Self-Directedness and neuroticism were also somewhat predictive of self-reported use of health care services for psychiatric reasons, and lifetime mental disorder. Moreover, high Harm Avoidance may associate with a family history of mental disorder.

Among MDD patients, the scores of the personality dimensions of neuroticism and extraversion were relatively stable during a depressive episode. However, neuroticism was strongly and extraversion less strongly dependent on the change in symptoms of depression, as along with recovery from MDE, the scores of neuroticism decreased and those of extraversion increased. Neuroticism, but not extraversion, was also somewhat dependent on the change in symptoms of anxiety. Thus, it might be difficult to get an accurate sense of a person's long-term personality traits during the acute phase of an affective disorder.

It seems that a depressive episode does not have a negative effect on an individual's personality. In the medium term follow-up of this study, a relapse or recurrence of depression did neither increase the patients' overall level of neuroticism nor decrease the level of extraversion, thus no scar in the personality dimensions of neuroticism or extraversion was observed.

The overall level of neuroticism was markedly higher and the level of extraversion slightly lower in depressive patients than in the general population, suggesting that especially neuroticism, but also extraversion might be a vulnerability factor or at least indicator for MDD. In clinical work, high neuroticism might be considered to be used as a risk indicator for a possible recurrence of MDD and to help making treatment plans e.g. when considering maintenance phase treatment for MDD.

Neuroticism and extraversion were found to be associated with the comorbidity of MDD and axis I and II disorders. A positive dose-exposure relationship was found between the level of neuroticism and the prevalence and number of comorbid axis I and II disorders. A

negative dose-exposure relationship was found consistently between the level of extraversion and social phobia and cluster C personality disorder, and less consistently with cluster A personality disorder. Patients with pure MDD, or with any comorbid axis I or II disorder, had positive standardized scores of neuroticism and negative standardized scores of extraversion, but the scores were not extreme in any patient group. This finding indicates that also other factors than neuroticism and extraversion are needed to explain the comorbidity patterns of MDD.

9.2 Implications for future research

Most of the existing studies on the relationship between personality dimensions and depressive and anxiety disorders have been conducted by using the two superfactors of neuroticism and extraversion. A more specific level of analysis and increased specificity of associations between personality domains and disorders would probably be gained by using subcomponents of neuroticism and extraversion, and also by using more than two personality dimensions.

Currently personality dimensions are mostly studied by using self-report questionnaires. In order to reduce the possible effects of mood and anxiety state and response style on the results, in future it should consider using also peer-ratings, semi-structured interviews and other methods e.g. the experience sampling method.

Most of the current prospective longitudinal studies on the connection of personality traits and affective disorders have been conducted among adolescents and adults. However, mood and especially anxiety disorders have often developed already by mid-adolescence. Thus, to truly test whether the temperament/personality dimensions predispose the affective disorders, longitudinal studies starting already in childhood should be conducted.

In future, when studying the comorbidity of MDD, alternative factors other than neuroticism and extraversion are probably needed to explain the comorbidity pattern. These factors might include not only the two personality dimensions of neuroticism and extraversion, but also other personality dimensions, disorder-specific genetic vulnerabilities, gene-environment interactions or distant (events or experiences from childhood and adolescence) and/or recent (stressful life-events and low social support) environmental risk factors.

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